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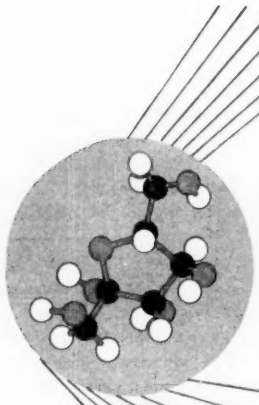

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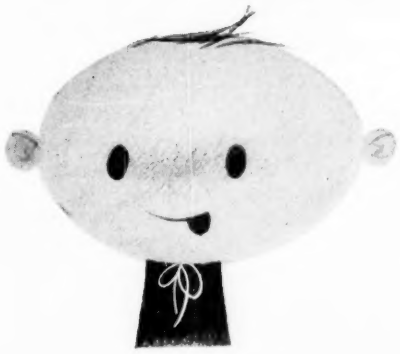

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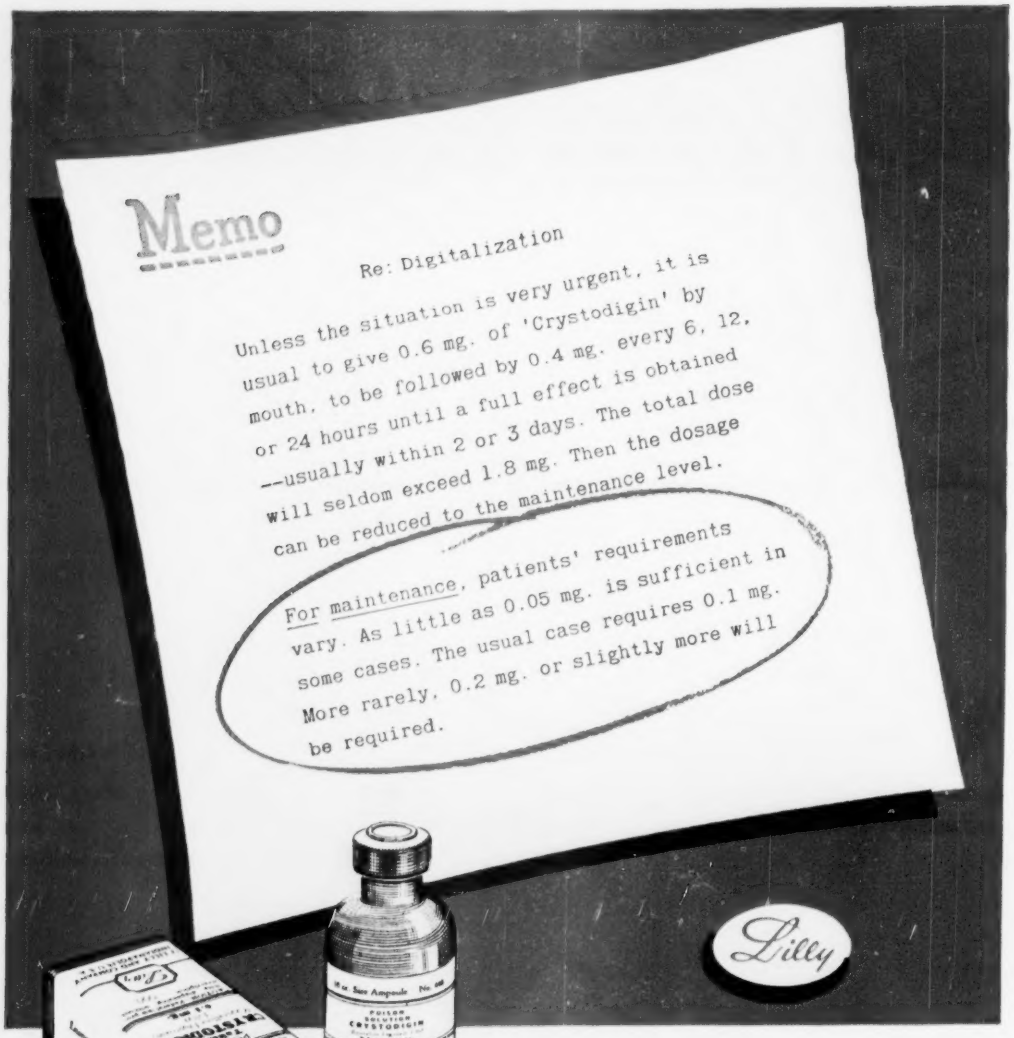
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Volume 249 DECEMBER 24, 1953 Number 26

HEPARIN TREATMENT OF PATIENTS WITH ANGINA PECTORIS*

Failure to Influence Either the Clinical Course or the Serum Lipids

H. L. CHANDLER, M.D.,† AND G. V. MANN, Sc.D., M.D.‡

BOSTON

THE treatment of angina pectoris for many years has been directed toward relief of the heart pain either by increasing the caliber of the diseased coronary arteries or their collaterals with vasodilators or by reducing the work load of the heart. The concepts relating atherogenesis to a defect of lipid metabolism have led to more ambitious therapeutic attempts to halt or even to reverse the development of atherosclerotic lesions in the vessel walls. After an association was found between elevated serum cholesterol levels and the precocious development of coronary atherosclerosis,[1-3] efforts were made to reduce the serum cholesterol levels, with the hope of preserving and improving the myocardial circulation. Restriction of dietary lipids[4] and treatment with lipotropic agents[5, 6] have been tried for such purposes. These relatively short-term experiments with man have been equivocal or have failed to demonstrate beneficial effects.

Gofman and his co-workers[7] have reported their conclusion that a significant positive correlation exists between atherosclerotic disease and high serum levels of certain classes of lipoprotein molecules as measured in the ultracentrifuge. Graham et al.[8] subsequently demonstrated that the parenteral administration of heparin resulted in immediate changes of the lipoprotein composition of the serum without affecting the serum lipids as measured chemically. Data confirming these transitory effects of heparin on serum lipoproteins have been published,[9] and it has also been demonstrated that the synthetic anticoagulant Treburon,§ when administered by the transbuccal route, has a similar action on the serum lipoproteins. In addition this medication lowers the level of the serum total cholesterol and phospholipid.

Graham and his co-workers[8] reported that parenteral administration of heparin inhibited the development of atherosclerotic lesions in cholesterol-fed rabbits that, judged on the basis of a parallel control series of animals, were expected to show such lesions. In addition these investigators described a dramatic effect of the treatment in alleviating the frequency and severity of heart pain in 55 of 59 patients with angina pectoris. A detailed description of the method of evaluation used in this study was not presented.

Subsequently Engelberg[10] reported favorable clinical results similar to those of Graham. In contrast Russek et al.[11] and others[12-15] found heparin ineffective in the treatment of angina pectoris. An experiment carried out to evaluate the effect of heparin upon the clinical course and the serum lipids of a group of patients with angina pectoris is described below.

METHODS

Patients with a characteristic history of angina pectoris were selected for this study. Angina pectoris was defined as paroxysmal, substernal pain of limited duration brought on by exertion alone or by exertion and emotional disturbances, and promptly relieved by rest or nitroglycerin tablets. Patients with other causes for chest pain were excluded from the series unless they were able to distinguish clearly the pain of angina pectoris from that of other causes. The selection, clinical management and observation of these subjects were made by one of us (H.L.C.).

Twelve men and 1 woman ranging in age from thirty-four to eighty-one years, with angina pectoris of two months' to six years' duration, were the subjects of this investigation. Although 13 subjects were studied, 14 courses of treatment were available for evaluation since 1 of the subjects entered the study a second time after a two-month interlude for a transurethral prostatectomy. None

*From the Fifth and Sixth Medical Services (Boston University), Boston City Hospital, and the Department of Nutrition, Harvard School of Public Health.

Presented in summary form at a meeting of the New England Cardiovascular Society, Boston, November 2, 1953.

Supported in part by the National Heart Institute, National Institutes of Health, Public Health Service, the American Meat Institute, Chicago, and the Nutrition Foundation, Incorporated, New York City.

†Instructor in medicine, Boston University School of Medicine; junior visiting physician, Boston City Hospital.

‡Assistant professor of nutrition, Harvard School of Public Health; associate staff member in medicine, Peter Bent Brigham Hospital.

§Treburon is the sodium salt of sulfated polygalacturonic acid methyl ester methyl glycoside.

of them were engaged in full-time, gainful occupation. The subjects were studied for periods extending from 7 to 13 months in a hospital outpatient department. A complete physical examination, x-ray examination of the chest and electrocardiogram were done on each. Although all subjects showed abnormal resting electrocardiograms, two-step tests with electrocardiograms as standardized by Master et al.[16] were performed repeatedly in 9 cases during the course of the study. After exercise, pain and changes in the electrocardiograms consistent with myocardial anoxia developed in 7 subjects. One subject had pain without electrocardiographic changes, and the other demonstrated neither electrocardiographic changes nor pain.

The subjects were observed for 1 to 4 weeks before the institution of any therapy. During this time examinations were completed, and the severity of angina pectoris was estimated. The subjects were familiarized with the simple report cards provided; these were similar to those described by Greiner et al.[17] The cards were used by the subjects to record daily the severity of the symptoms of angina pectoris. Opportunity was provided to describe the heart pain each day as "usual," "worse," "very bad," "better" or "no attacks" by a check mark in the appropriate block on the report card. The number of nitroglycerin tablets* used each day was also recorded.

After this preliminary period of examination all subjects received 10 cc. of a placebo intravenously twice weekly at intervals of 3 or 4 days. The placebo used was a 5 per cent solution of glucose in water. For the first week of the placebo treatment the clinician knew what medication the subjects were receiving, but the subjects were led to believe that they were receiving possibly effective therapy. At varying times thereafter, which were selected at random, 100 mg. of heparin† dissolved in 10 cc. of water was substituted for the placebo by an assistant. The time of this substitution was not known to either the subject or the clinician. During the last 2 or 3 months of the study clinic visits and treatments were arranged on a weekly instead of a semiweekly basis. Examination of the data disclosed no change in any subject's course as a result of this modification.

*The tablets used contained 0.4 mg. of nitroglycerin.

†Kindly supplied by the Upjohn Company, Kalamazoo, Michigan.

The preliminary periods of placebo administration were continued for 10 to 91 days in various subjects for a total of 867 subject days of this treatment. Heparin treatment was then given over periods of 28 to 151 days for a total of 1329 subject days or a mean of 95 days per subject. All except 3 subjects received heparin treatment twice weekly throughout the entire period of its administration. In these 3 the heparin treatment was given twice weekly for intervals of 18, 80 and 80 days and thereafter once weekly for 84, 32 and 25 days respectively. All the subjects except these 3 and 1 other were observed during another post-heparin period of intravenous placebo treatment administered either once or twice weekly for periods ranging from 25 to 168 days for a total of 1117 subject days.

At every clinic visit the clinician questioned each subject, and noted the relation between the heart pain and the subject's activity and environment. During the preliminary period before parenteral treatment was started, blood was drawn from each subject for serum lipoprotein determinations, performed by the method described by Gofman et al.,[7] and for analysis of serum total cholesterol, by the technic of Abell and her associates.[18] At intervals of approximately a month thereafter, and just before the administration of the intravenous therapy of that visit, blood samples were taken for repetition of these measurements. Initially a modified Lee and White clotting time[19] was measured with this blood, but because no abnormalities were found during the first several months this procedure was discontinued.

Table 1. *Sample Periods Chosen from the Total Course of Therapy of Each Subject.**

Treatment	Initial Placebo		Heparin		Placebo after Heparin
Average duration of treatment	62 days for 14 courses		95 days for 14 courses		112 days for 10 courses
Period	1	2	3	4	5
Sample	1st 28 days	Last 28 days	1st 28 days	Last 28 days	Last 28 days

*For each subject there was a variable interval of continued treatment between the first and second, the third and fourth and the fourth and last sample periods.

Results

Clinical Evaluation

For the purpose of clinical evaluation, consideration was given to the following classes of collected data: the subjects' oral reports; the weekly nitroglycerin intakes computed from the subjects' daily records; the percentage of "better" and "worse" days so far as chest pain was concerned, as computed from the subjects' report cards; repeated two-step tests; and a judgment of the clinician based on an analysis of all the information available.

To facilitate presentation of the results of this experiment, samples of the voluminous data available were considered. For this purpose the total

time of treatment for each subject was divided into the three major periods of initial placebo therapy, heparin therapy and post-heparin placebo therapy. As indicated in Table 1 the sample periods chosen for evaluation were the first and last 28 days of both the initial placebo therapy and heparin therapy, and the last 28 days of placebo therapy after heparin (Table 1).

Subjects' oral reports. During the course of the study, 11 of the 13 subjects were enthusiastic about the improvement they experienced. Several reported relief from anginal attacks at night, most were impressed with the decreased frequency and severity of pain, and many believed that their tolerance to exercise had increased. Of the 11 subjects who described improvement at some time during the study, 7 reported consistent, progressive relief starting within the first four weeks of placebo treatment. Two additional subjects stated that they felt appreciably improved later than the first month but still this improvement occurred during their initial periods of placebo administration. Two subjects first experienced relief during the time they were receiving heparin intravenously. In one of these subjects heparin was started after only 18 days of placebo treatment.

In all subjects, regardless of when improvement was first experienced, it continued for the remainder of the total period of observation. There were fluctuations from time to time in the degree of relief, as expressed in interval interviews, but there was no sharp change for the better associated with the introduction of the heparin treatment. The subjects' oral reports indicated that they were unable to discriminate between placebo and heparin treatments by symptomatic improvement.

Nitroglycerin intake. The subjects' professions of relief from pain were supported generally by evidence of decreased nitroglycerin intake. However, these professions of improvement often did not coincide with decreased need for this medication. Although there was wide individual variation in the range of decreased nitroglycerin consumption, even in subjects with about the same initial level, all subjects reported more or less regular decreases of requirement for this medication.

Figure 1 shows the changes in the number of glyceryl trinitrate tablets used weekly during the sample periods of Table 1. Most subjects had obtained maximal relief as judged by this criterion during the preliminary period of placebo administration. There was little evidence of any additional benefit attributable to the heparin treatment.

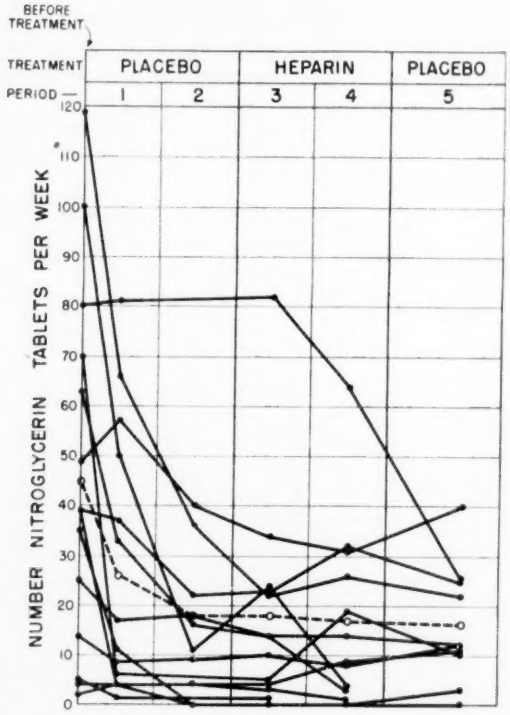

FIGURE 1. *Influence of Placebo or Heparin Treatment on Each Subject As Reflected by the Recorded Weekly Intake of 0.4-Mg. Tablets of Nitroglycerin.*

The broken line represents the mean response of all 14 courses of treatment. The curve starting at 80 describes the subject in whom periods 1 and 2 comprised only 18 days.

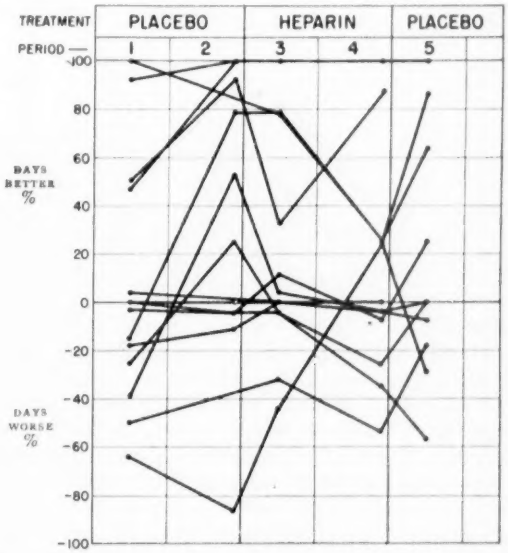

FIGURE 2. *Influence of Placebo or Heparin Treatment As Reflected by Each Subject's Daily Report of His Condition.*

The percentage of days of improvement as positive were added algebraically to the percentage of days of worsening as negative, without weighting for degree of change.

Report cards. The report-card data were evaluated after the subjects' interpretations of their condition had been condensed into two classes. For this purpose the number of "better" and "no attack" days were summed as one class (positive), and the "worse" and "very bad" days were summed as the other (negative). No weighting was introduced to describe the degree of change, and the days reported as "no change," which are not here considered, constitute the remainder of the exposure days.

To demonstrate trends of response with changes of treatment a diagram using the data from the sample periods described in Table 1 for all the subjects treated was constructed (Fig. 2). In 8 of 14 courses of treatment improvement was reported during the initial placebo period. In 2 there was no change of symptoms, and in 4 the condition became worse. During the first month of heparin treatment 4 subjects indicated improvement, and 4 showed worsening of their anginal attacks, whereas 6 indicated no change. During the remainder of heparin treatment the trends were toward aggravation of symptoms in 8 subjects, improvement in 2 and no change of symptoms in 4. Of the 10 subjects observed during the final period of placebo treatment, 6 described improvement, 1 was unchanged, and 3 reported worsening of their condition.

The data of the 10 subjects who completed all three periods of treatment were considered in detail (Table 2). There were available 632 subject days of initial placebo treatment, 984 subject days of heparin treatment and 1117 subject days of post-heparin placebo treatment.

The ratios of the "better" days to the total days of exposure were computed for each subject and for each of the successive treatments. Subtraction of these ratios for the initial placebo treatment from the heparin treatment and for the last placebo treatment from the heparin gave differences that were then evaluated by the use of a conventional "t" test. The same procedures were applied to comparisons of the influence of the treatments upon the observed frequencies of "worse" days. With the exception of a diminished frequency of "worse" days in the heparin treatment period ($t = -2.40$, $p < 0.05$), all comparisons revealed differences attributable to sampling variation with probabilities of 5 per cent or more.

Two-step tests. Twenty-six "two-step" tests on 9 subjects were performed at intervals during the study. The tests during the heparin phase of treatment were carried out from 4 hours to 2 days after the last injection, and 3 to 16 weeks after the start of this therapy. Five subjects underwent the tests during the initial placebo period and again while heparin was being administered. The others were tested first during heparin treatment and again 1 to 4 months after the heparin therapy had been stopped. There were no demonstrable effects of any treatment upon the electrocardiographic responses of these subjects although in 1 the amount of exercise completed before the intercession of pain was slightly greater during heparin treatment than it was before or after.

Total clinical evaluation. An evaluation was made on the basis of an analysis of each subject's course utilizing all the available data noted above, and modified by a knowledge of intercurrent environmental factors influencing each subject's condition. The analysis was made originally without knowledge of the therapy schedule. By this evaluation 8 subjects experienced definite improvement during the experiment — a generally progressive reduction in the frequency and severity of heart pain and greatly reduced nitroglycerin requirements. On subsequent comparison with changes of therapy the rate and degree of improvement was found not to have been influenced by the change from placebo to heparin or from heparin back to placebo treatment. Sharp changes, for either the better or the worse, lasting from a week to a month or more were often related to various mental, physical or environmental factors.

TABLE 2. *Evaluation of the Influence of Placebo and Heparin Treatment on the Clinical Course of Angina Pectoris as Judged by the Daily Report Cards of 10 Subjects Who Completed All Phases of the Study.*

Subject No.	Placebo			Heparin			Placebo		
	days *total*	worse *total*	better *total*	days *total*	worse *total*	better *total*	days *total*	worse *total*	better *total*
1	77	0.25	0.21	98	0.15	0.19	147	0.29	0.21
3	18	0.50	0.00	84	0.44	0.00	168	0.29	0.00
4	20	0.05	0.70	151	0.01	0.54	56	0.02	0.57
6	87	0.20	0.07	98	0.01	0.00	147	0.04	0.00
7	91	0.24	0.47	98	0.11	0.62	147	0.05	0.86
8	52	0.10	0.06	91	0.25	0.09	25	0.52	0.00
9	70	0.04	0.93	84	0.00	1.00	63	0.00	1.00
10	84	0.26	0.20	98	0.04	0.03	147	0.02	0.00
11	42	0.74	0.00	84	0.36	0.64	63	0.33	0.31
12	91	0.13	0.18	98	0.08	0.87	154	0.11	0.65

One subject became ill on the 56th day of the final placebo treatment and died 14 days later. He had previously received heparin treatment twice weekly for a period of 115 days. The clinical diagnosis at the time of death was myocardial infarction complicated by pulmonary infection. No autopsy was performed.

No hemorrhagic complications or other untoward side effects resulted from the intravenous administration of 100 mg. of heparin twice weekly for periods up to 151 days to these ambulatory patients.

Laboratory Results

The lipoprotein and cholesterol measurements on the serum of these subjects were studied according to the treatment periods (Table 3). For this purpose the values obtained during each treatment were averaged for each person. Inspection of data for individual subjects, as well as the tabulation of the means of all subjects for each treatment period, gave no evidence that the heparin treatment led to any significant changes in either the serum cholesterol or any class of serum lipoproteins measured. Blood was always drawn for analysis 3 or 4 days after the last injection of heparin. With intravenous injections of 100 mg. of heparin twice weekly there was no persistent effect on these lipoprotein classes for the interval of 3 or 4 days between injections, nor was any cumulative effect from prolonged treatment identifiable.

TABLE 3. *Average Serum Lipoprotein and Cholesterol Levels of Subjects with Angina Pectoris during 14 Courses of Parenteral Treatment with Either a Placebo or Heparin.*

Subject No.	S_f12-20			S_f20-100			Cholesterol		
	Placebo before heparin	Heparin	Placebo after heparin	Placebo before heparin	Heparin	Placebo after heparin	Placebo before heparin	Heparin	Placebo after heparin
	mg./100 cc.	mg./100 cc.	mg./100 cc.	mg./100 cc.	mg./100 cc.	mg./100 cc.	mg./100 cc.	mg./100 cc.	mg./100 cc.
1	66.0	94.0	73.3	132.0	202.0	154.0	317	336	303
2	38.5	44.5	—	41.0	51.5	—	216	228	—
3	69.5	46.7	51.0	267.0	174.0	171.0	280	216	228
4	46.0	45.6	56.0	50.5	41.0	28.0	206	197	171
5	13.0	10.5	—	24.5	13.5	—	158	157	—
6	29.8	42.0	37.3	43.0	69.0	82.0	283	299	295
7	46.5	36.5	42.0	97.0	92.5	86.0	190	179	188
8	79.7	91.0	110.0	115.0	139.0	108.0	269	311	294
9	50.2	78.5	71.0	130.0	145.0	350.0	219	280	287
10	45.0	38.2	39.0	60.7	44.0	45.0	282	296	279
11	20.3	27.0	31.0	54.7	53.0	50.0	276	299	274
12	52.3	60.5	53.5	150.0	110.0	114.0	230	250	248
13*	32.5	29.0	—	116.0	72.0	—	261	243	—
14*	37.3	39.0	—	164.0	67.0	—	263	252	—
Means ± Standard Deviations	44.8±18.4	48.8±24.2	—	103±65.2	90.9±55.4	—	247±44.1	253±53.5	—
	50.5±17.9†	56.0±23.9	56.4±23.4	110±67.5	107±56.7	119±93.4	255±40.8	266±53.1	257±46.8

*Subject No. 13 and 14 was the same person, observed during two separate courses.
†The data of the 10 subjects who completed all 3 phases of treatment.

Discussion

There is general acknowledgement of the difficulties involved in evaluating the effects of any therapy in angina pectoris. Psychic, somatic and environmental factors may alter susceptibility to pain, each in varying degree and direction. Furthermore, since each patient demonstrates a different combination and extent of these devious factors, comparing one patient with another or a grouping of them may lead to erroneous conclusions. Because of this variability from patient to patient, in studies of the effect of treatment on the manifestations of angina pectoris, some knowledge of the range of reaction of each patient must be known to the investigator, and each subject should serve as his own control. No single criterion of condition appears to be an adequate measure of the effect of medication, and some criticisms may be directed toward each of those proposed.

The use of report cards, as discussed by Greiner et al.,[17] was found to have certain definite limitations. Each subject was asked to record his current condition as the study progressed, using his "usual" status before the trials started as a standard of reference. Even during the preliminary period before treatment most subjects reported many more days of "worse heart pain," "very bad" or "better" days than those of "usual heart pain," indicating considerable variability from day to day. A "usual" status was thus recognized with difficulty. Though this record may be expected to have some relative value, the standard of reference of many subjects became blurred as the study progressed. There was often a tendency for the subjects to magnify the severity of the past distress in their recollection. There was reason to believe that they did not use their pre-study condition for reference each time the cards were marked although this was emphasized to them repeatedly. It appeared that they compared each day with a general impression of how frequent and severe their heart pain had been a few days or a few weeks before.

The advantages of simplicity and apparent objectivity of this method of evaluation are vitiated by the unreliability of the basic data. Since these data are easily reducible to quantitative terms, they are readily susceptible of statistical handling. As noted above, because of the many variables among subjects, such a manipulation may compound the errors and lead to a false conclusion, elaborate as the statistical treatment may seem. If the daily condition reports have any validity, the improvement indicated by the significantly fewer worse days occurring during the period of heparin treatment reflects merely the benefits conferred by the procedure of the study itself.

The course of weekly intakes of nitroglycerin tablets was probably the most accurate single measure of condition change since the vagaries of memory were not introduced and the perceptions leading to nitroglycerin medication may be expected to be relatively constant. This conclusion is limited by the assumption that such patients take nitroglycerin tablets only when they have chest pain. The nitroglycerin intakes (Fig. 1) were the most consistent of the measures and served to demonstrate that the first treatment in such an experimental plan occupies a unique position of favorability of response. A failure to recognize this experimental artifact might easily lead to incorrect conclusions in the evaluation of a treatment. Four subjects indicated both by their verbal estimates and by report cards that their conditions progressively improved well into the post-heparin placebo period. The rate and extent of this decrease in anginal pain is shown for each subject in Figure 1. If these curves were drawn on a weekly basis, they would generally be irregular and would vary in slope and time of flattening out. Neither the extent nor the rate of change described by such curves appeared to be altered by the substitution of heparin for placebo. About 100 days of parenteral therapy elapsed for most of these subjects, previously treated in a general medical outpatient clinic, before they achieved maximal improvement. This improvement appeared to be independent of the kind of treatment. The striking improvement in most cases while the subjects were on placebo treatment emphasizes the importance of frequent visits to an interested physician and the powerful effect of parenteral therapy in this disease.

The "two-step" tests done during the course of the treatments did not indicate a beneficial effect of heparin treatment upon the manifestations of angina pectoris measured by this test.

Treatment twice weekly with 100 mg. of heparin intravenously did not demonstrably alter the serum lipoproteins or cholesterol. Previous studies[8, 9] have revealed that such a treatment does lead to a transitory reduction of the S_f20-100 and S_f12-20 classes of lipoprotein in serum. The present studies indicate that there is no cumulative effect of serial intravenous treatment with heparin when this is administered at intervals of 3 or 4 days. The anomalous results of Rinzler et al.,[13] who observed "significant" reductions of certain classes of serum lipoproteins with placebo treatment but not with heparin treatment, is readily explained by the noncomparability of initial lipoprotein levels in the two groups studied. Their experience emphasizes the importance of either using matched groups or proceeding with an internally controlled experiment.

Summary

Eleven of thirteen subjects with angina pectoris experienced moderate to marked relief after the intravenous injection twice weekly of 10 cc. of placebo solution consisting of 5 per cent glucose in water. The substitution of 100 mg. of heparin dissolved in 10 cc. of water for the glucose solution provided no advantage over the use of the placebo in alleviating heart pain.

About 100 days of parenteral treatment was required for most of these subjects to achieve maximal improvement.

This treatment had no persistent or cumulative effects on either the serum cholesterol or the serum S_f12-20 or S_f20-100 classes of lipoprotein.

The intravenous injection of 100 mg. of heparin in ambulatory patients twice weekly for periods up to 151 days and for a total of 1323 patient days was accompanied by no hemorrhagic disturbances or other untoward effects.

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EFFECTS OF ISONIAZID ON PATIENTS WITH TUBERCULOSIS AND MENTAL ILLNESS

BLAIR HUNT, M.D.,* AND JOSEPH D. WASSERSUG, M.D.†

BOSTON AND QUINCY, MASSACHUSETTS

AFTER the favorable early reports[1, 2] on the use of isonicotinic acid hydrazide (isoniazid) for the treatment of tuberculosis, therapy with this drug was begun for a group of psychotic patients in the tuberculosis isolation building of the Boston State Hospital. In earlier descriptions of the mood change of patients incident to isoniazid therapy, "a subtle, general stimulation" of the mood was noted.[2] One could not tell, however, from the initial investigations, whether the "stimulating" effect was secondary to reduction in patients' toxicity or whether isoniazid, in itself, had a euphoric action. The question was therefore raised whether some of the helpful effects of the new drug were due to elation of mood or whether mood changes were the result of physical recovery.

More recent reports[3] also fail to be specific about these points although the impression is gained that diminution in toxicity antedates the return of a sense of well-being. Selikoff, Robitzek and Ornstein[3] make the following observation:

> Appetite begins to improve, especially when it has been poor, as early as the second day of therapy, and improvement is almost always noted by the end of the first week. At this time, return of strength, energy, and sense of well-being begins to become manifest, and improvement is marked by the end of three weeks. This reversal of systemic toxicity is more marked in toxic cases, and may be seen even in moribund patients.

In another survey, dealing with 390 patients and set up by the directors of 22 tuberculosis hospitals, co-ordinated through a central office in the United States Public Health Service, the effects of isoniazid were determined in a controlled experiment in which random selection of patients was assured.[4] It was concluded that "isoniazid appears, at the least, an extremely effective antituberculous agent for short-term therapy." No note was made, however, in this extensive report, on the effect on patients' moods.

One study[5] deals specifically with the effects of isoniazid in the tuberculous insane. In this report, 48 patients were carried through a course of isoniazid therapy for ninety days; some degree of appetite improvement was seen in more than two thirds of the patients treated. Although patients were selected for study on the basis of their tuberculosis and not on that of their psychosis, some degree of change in mental behavior was noted in 21 of the 48 patients studied, being marked in 6, moderate in 12 and slight in 3. Twenty-seven patients failed to show any degree of mental improvement.

Since improvement had not been anticipated when the investigation was begun, suitable controls were not included in the study. The authors, however, regarded the improvement as more than a temporary feeling of euphoria or increased sense of well-being and as actually representing a renewed contact with reality in some patients who had been withdrawn and hallucinative for a long time. Many patients showing no change in mental behavior were only mildly psychotic and displayed no gross evidence of psychosis. The authors add:

> We should like to call attention at this time to the fact that the greatest degree of improvement occurred, as a general rule, among patients with a diagnosis of schizophrenia, without any significant relation to the type. Since it is not our purpose here to assume the role of the psychiatrist but rather to point out that we have observed a change in mental behavior which we feel is directly related to the administration of isonicotinic acid hydrazide, individual case reports have not been included. We are simply reporting these changes in the hope that we may stimulate an interest in further research into this interesting phenomenon.

In May, 1952, shortly after the appearance of reports on the use of isoniazid, this drug was included in the general therapeutic program of the tuberculosis unit so that during the period covered by the present report (May, 1952, through March, 1953) 78 patients received this agent; the results are considered below. Since the diagnosis of tuberculosis was made by x-ray findings in 17 patients, who were started on isoniazid before or without the finding of acid-fast bacilli, they are not evaluated for change in pulmonary status but are included in the evaluation of change in mental status.

Eventually, isoniazid‡ became the first treatment in all newly discovered cases of pulmonary tuberculosis as well as in tuberculous patients who had not responded favorably to other agents. It replaced streptomycin in 7 cases in which that antibiotic had failed to produce improvement —

*Assistant physician, Boston State Hospital.

†Instructor in medicine, Tufts College Medical School; visiting physician in tuberculosis, Boston State Hospital; acting physician, Quincy City Hospital.

‡Kindly supplied by Hoffmann-La Roche, Incorporated, Nutley, New Jersey, under the trade name, "Rimifon."

with improvement subsequently noted in 6. In 21 cases streptomycin was combined with isoniazid, when initial improvement with isoniazid was not sustained. Four patients who were receiving streptomycin were also given PAS.

The dosage of isoniazid approximated 4 mg. per kilogram of body weight. For convenience of administration, the dosage was standardized at 100 mg., three times a day, after meals. In 9 cases this dosage was increased to 200 mg., three times a day, after reports of increased benefit with larger doses. The dosage of streptomycin, when it was used in conjunction with isoniazid, was 1 gm. twice a week. For 3 patients operated on during this period streptomycin dosage was increased to 2 gm. a day for two weeks after operation. The dosage of PAS (used in 4 cases only) was 12 gm. daily in four divided doses.

In addition to these drugs, medical or surgical treatment was continued or instituted for each individual case, as was specific or nonspecific psychiatric therapy.

The duration of treatment for individual patients during the period reported on ranged from ten to three hundred days, with an average of one hundred and sixteen days. Except for 2 terminal cases, in which the patients died ten days after isoniazid was begun, the shortest period of treatment was thirty days.

Of the 78 patients, 58 were men, and 20 women. White patients numbered 74, Negro 3, and Chinese 1. The age range was twenty-one to eighty-four years, with an average age of forty-eight years.

Duration of pulmonary disease (as determined by date of discovery) before therapy with isoniazid varied from two days to twenty-five years, the former in a patient whose chest film and physical examination on admission constituted discovery. The average duration was four and one tenth years.

Duration of hospitalization for mental illness, as determined from date of this present admission to the hospital to the end of the period reported, varied from two days to thirty years, the average being nine years. The mental diagnoses of these patients are presented in Table 1.

The criterion for selection of patients for therapy was x-ray appearance suggestive of active pulmonary tuberculosis. Positive sputums were obtained on 59 of these 78 patients. Of the other 19 patients, 2 had extrapulmonary tuberculosis, and treatment with isoniazid was started on the remaining 17 without positive sputums because of x-ray and clinical evidence of possible activity. Eleven of this group of 17 showed patterns of clearing on the x-ray films, as well as clinical improvement, even though the sputums were never positive.

The remaining 6 of the group without positive sputums are included, although they may not have had active tuberculosis, because this report covers changes in mental condition consequent to isoniazid therapy, as well as changes in tuberculous disease. The 17 patients who did not have positive bacteriologic findings are not included for discussion under changes in tuberculosis but are only under consideration for possible changes in mental status.

Of the 59 cases of active pulmonary tuberculosis, 1 was minimal, 25 moderately advanced, and 34 far advanced. In the 2 extrapulmonary cases, 1 patient had tuberculous proctitis, and the other had tuberculous spondylitis and nephritis. Four patients were moribund, with extensive disease, when isoniazid therapy was begun.

TABLE 1. *Mental Change in Patients on Isoniazid Therapy.*

DIAGNOSIS	NO. OF PATIENTS	IMPROVEMENT	REMISSION	DEATHS
		NO. OF CASES	NO. OF CASES	NO. OF CASES
Schizophrenic reaction:				
Paranoid type	6	0	0	0
Catatonic type	10	0	0	1
Hebephrenic type	11	0	0	0
Simple type	4	0	0	0
Chronic, undifferentiated type	10	0	0	0
Paranoid state	6	0	0	0
Affective reaction	1	0	0	0
Mental deficiency (psychotic reaction)	2	0	0	0
Chronic brain syndrome:				
Associated with mongolism (mental deficiency)	1	0	0	0
Associated with cerebral arteriosclerosis	2	0	0	0
Associated with circulatory disturbance (congestive heart failure)	2	0	0	0
Associated with senile brain disease	2	0	0	0
Associated with alcohol intoxication (Korsakow's psychosis)	10	6	0	1
Acute brain syndrome associated with systemic infection (pulmonary tuberculosis)	6	1	4	1
Involutional psychotic reaction	1	0	0	0
Sociopathic personality disturbance (with psychotic reaction)	3	0	0	1
Without psychosis (recovered from postoperative schizophrenic reaction)	1	0	0	0
Totals	78	7	4	4

Two patients were diabetic, requiring 20 and 50 units of NPH insulin respectively. One patient with arteriosclerotic heart disease with cardiomegaly and 2 with hepatic cirrhosis with ascites required treatment for these conditions as well as for their pulmonary tuberculosis.

The treatment and progress were evaluated on the basis of the following criteria: roentgenographic changes, appetite, weight, temperature, bacteriology, mental status and side reactions.

Results of Therapy

Roentgenographic Changes

Favorable x-ray changes were noted in 42 of 57 patients, or 73 per cent. Two of the 59 patients with pulmonary tuberculosis had thoracoplasty, and a third, who had thoracoplasty, had clearing of the contralateral lung. The favorable change ranged from cavity closure, which was noted in 9 patients, to clearing of infiltrates, and decrease in cavity size. Nine patients showed no change, and in 6 cases x-ray examination revealed progressive worsening.

Appetite

Change in appetite was not easy to evaluate, but certain general observations could be made. In the first place, almost all patients who were toxic, with temperature elevations over 100°F., improved remarkably in appetite. This was true even of 3 moribund patients who died in spite of treatment. The very toxic patients, in some cases, showed appetites that could be called "ravenous." They consumed two or three helpings at each meal shortly after the start of treatment. As temperatures went down and signs of toxicity disappeared, their appetites became more normal, and they continued to eat well, but not ravenously.

These observations were complicated by the fact that some patients demonstrated fluctuation in their desire to eat for reasons that were obviously emotional rather than due to anorexia because of tuberculosis. For example, a patient with cavity closure and conversion of bacteriology by gastric culture continues to have a poor appetite, on occasion refuses to eat or eats only scraps from other patients' trays. Another severely withdrawn catatonic patient has shown x-ray clearing but must be spoon fed.

Weight

Change in weight was consistent with x-ray clearing. Of 49 patients who could be followed with weight records, 40, or 81 per cent, gained weight. Three patients remained the same, and 6 patients lost weight. Twelve patients could not be followed with weight records, being either too moribund or unable to be weighed for other reasons.

Temperature

Significant afternoon temperature elevation (99.6°F. or higher) was noted in 16 patients at the start of treatment. Reduction in temperature elevation was noted in 12 of these. Four moribund patients who died showed initially a drop in temperature, but temperatures again rose.

Bacteriology

Of the 59 patients with positive bacteriologic findings — that is, either positive sputum by direct smear or culture or positive gastric by direct smear and culture — not all could be re-evaluated during the time of this report. Only 18 were consistently followed so that a sputum or gastric was taken some time before the end of the period reported. Of this number, 12 showed conversion. Of the 2 patients with extrapulmonary tuberculosis, 1 with nephritis showed a conversion in urine cultures; the other left the hospital, his psychosis having undergone remission, to be continued in treatment for his tuberculous proctitis at another hospital (remission of the psychosis had begun before isoniazid was started).

Each of the cases of conversion in bacteriology showed x-ray changes consistent with arrested tuberculosis.

Mental Status

Evaluation of mental status was made on the basis of general appearance and behavior, stream of talk, mood, mental content, intellectual functions, orientation, apperception, insight and judgment. All 78 patients who were given isoniazid received this evaluation. Changes in mental status were noted in 11 patients while they were on isoniazid therapy.

Four patients with the diagnosis of acute brain syndrome associated with tuberculosis, schizophrenic reaction, showed a remission of the psychosis while on medication with isoniazid.

The following case reports are representative of these 4:

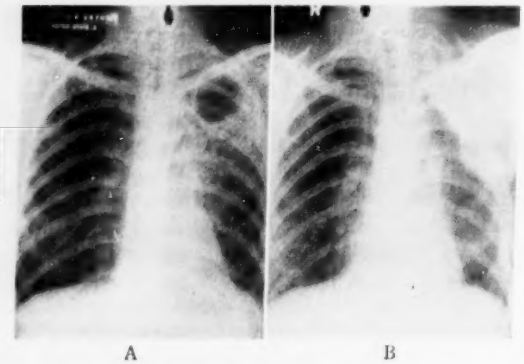
G. T., a 37-year-old married woman, was admitted to the Boston State Hospital on March 23, 1952. She was said to have become suddenly excited, violent and depressed; for 48 hours she had been crying and screaming. The patient had 5 children, with a normal delivery of the 5th 3 weeks before admission. No previous history of tuberculosis was given.

On admission she was confused, overactive and disturbed; at times she cried, and at others she burst into inappropriate laughter. On the ward she was unco-operative and destructive, tearing her clothes off and her bedding. This disturbed behavior continued for the 1st 4 months. She slept only with sedation.

The temperature was elevated on admission and fluctuated from 100 to 102°F. for the next 4 months. X-ray study showed soft infiltration throughout the left-upper-lung field and a large 5-cm. cavity at the level of the 1st rib (Fig. 1*A*).

The patient was placed on streptomycin for 3 months, without significant change. Attempt at left pneumothorax was unsuccessful. On isoniazid therapy, within 3 weeks the temperature subsided to normal levels, appetite improved, and she became quiet, co-operative with personnel and pleasant, but still slightly de-

pressed. The depression lifted completely in 2 more weeks, and for the rest of her hospital course she showed quite appropriate affect and was co-operative for all further procedures. Her behavior, which had been destructive and denudative, changed so that the was a very neatly dressed, pleasant woman. Her



A B

FIGURE 1. *Roentgenograms in G. T., Showing Infiltration and Cavity Formation* (A) *and Appearance after Isoniazid Therapy, Lobectomy and Thoracoplasty* (B).

stream of talk, which had been incoherent and flighty, became a modest, pleasant, inquiring manner of speaking.

Subsequently the left upper lobe was excised and a thoracoplasty performed since she had a tension cavity that did not close. Streptomycin and PAS, as well as penicillin, were added to the isoniazid medication for these operative procedures. She was released from the hospital 4 weeks after the 2d operation and 1 year after admission. Two gastric cultures were negative after operation; this case was classified as pulmonary tuberculosis, arrested. The operative procedures showed a good result (Fig. 1*B*).

M. G., a 30-year-old Negress, a clerical worker, married but without children, was discovered to have tuberculosis in October, 1951, and was admitted to a sanatorium, where she became so withdrawn and despondent, refusing to eat or talk and suffer-

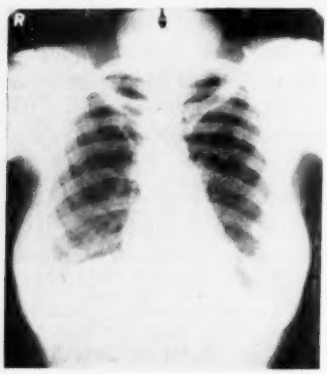


FIGURE 2. *Roentgenogram in M. G. after Two Months of Isoniazid Therapy.*

ing from hallucinations, that she was committed to Boston State Hospital after 1 week. She was placed on streptomycin, and pneumoperitoneum was induced, but she was resistive, negativistic and even destructive of equipment to such an extent that this procedure was discontinued. She was not responding to streptomycin, and her prognosis seemed extremely poor. She had a 5-cm. cavity in the left upper lobe, with infiltration at the base and spread to the right-middle-lung field. In her 18th month in the hospital she was placed on isoniazid therapy, streptomycin being discontinued. One month after isoniazid therapy had been started her behavior showed marked improvement. She became talkative and co-operative. Her depression lifted and she wanted to know why she was being kept in the hospital. At the same time, her appetite improved, and she gained 20 pounds in 2 months. In the same 2 months, x-ray evidence of the large cavity in the left upper lobe disappeared completely, and there was clearing in both lung fields, only small linear densities remaining (Fig. 2). She remained in the hospital for 2 more months, during which, although her psychosis was in remission, she was a management problem. She insisted she was being wrongly detained, refused to believe that she had been severely ill, mentally and physically, and demanded that she be released immediately. Finally, she was released to her husband for a trial visit at home, with instructions to continue isoniazid. Culture of gastric content on release from the hospital was negative for the tubercle bacillus. She returned to the hospital during the ensuing 6 months for follow-up care. She went back to work after being out for 2 months. The x-ray film shows no exacerbations, and there has been no return of clinical symptoms. She has been co-operative about outpatient visits, and her rapport with her psychiatrist became much better after she left the hospital. After seeing her x-ray films she no longer regarded her hospitalization as an incarceration.

These cases were diagnosed as acute brain syndrome associated with systemic infection (pulmonary tuberculosis). Seven cases in the series were similarly diagnosed. Except the 1 fatal case, all patients improved mentally. On the other hand, there were 41 patients with schizophrenic reaction who had shown this regressive pattern long before signs of pulmonary tuberculosis appeared; they continued to be schizophrenic.

The following case of chronic schizophrenia (incidentally, the least chronic, since the duration of the schizophrenia based on the time of hospitalization was the shortest of the 41 similar patients) did not show improvement while on isoniazid in contrast to the 2 cases presented above.

H. L., a 38-year-old married woman, was admitted to Boston State Hospital from another psychiatric hospital when her admission chest film showed densities suggestive of active pulmonary tuberculosis. The diagnosis was schizophrenic reaction — catatonic type. She had had 4 episodes of catatonic withdrawal in the past 3 years. At home, she had stopped doing her housework, stopped talking and refused to eat. One electric-convulsive treatment at the first hospital resulted in her beginning to eat again. On admission to Boston State Hospital gastric culture was positive. X-ray examination showed nodular densities in the left-upper-lung field, and the pulmonary tuberculosis was classified as minimal. Streptomycin was started and continued for 7 months. Then for 4 months, the patient received isoniazid alone. X-ray examination showed gradual clearing during the 11-month period; gastric cultures became negative, and at the end of this period she was released on a trial visit at home as a case of arrested tuberculosis. Although she was somewhat more talkative and outgoing than on admission she was still actively schizophrenic.

This patient showed no essential mental improvement on medication with isoniazid. Her depression had lifted while she was receiving streptomycin, but prescription of isoniazid did not improve her mental status, although the x-ray films continued to show clearing. She reached a plateau before starting isoniazid and improved no further. The course on isoniazid therapy was very much the

same as that of the other patients with chronic schizophrenia who were on it: there was no real change in the essential psychotic process.

The 2 patients previously discussed (G. T. and M. G.) demonstrated a change and a clear-cut remission of psychosis, corresponding with the improvement in the tuberculosis and alleviation of marked systemic toxicity. On the other hand, their psychoses were apparently precipitated by their tuberculosis, whereas in H. L. there was a long history of schizophrenia of at least three years' duration before the x-ray findings.

Another case of 1 of the 41 chronic schizophrenic patients in this series illustrates the improvement of a far-advanced case of pulmonary tuberculosis on isoniazid alone, with no essential improvement in the psychotic process.

G. L., a 24-year-old man, was admitted to Boston State Hospital in 1936. He presented a picture of a schizophrenic reaction, catatonic type. He was discovered to have pulmonary tuberculosis in 1949 by x-ray examination. His sputum was positive by direct smear. He received streptomycin and pneumoperitoneum, without improvement. Isoniazid was started in May, 1952, and continued without other medication during the 10 months of the survey. He gained weight, and gastric culture was negative for acid-fast bacilli after 10 months. In addition, he showed x-ray clearing of multiple cavities that had been evident at the beginning of isoniazid therapy (Fig. 3*A* and *B*). At the end of the survey period, the tuberculosis was considered arrested, but his disordered, bizarre, withdrawn behavior continued in spite of a concurrent series of 18 electric-shock treatments instituted in the hope of improving the impulsively assaultive behavior.

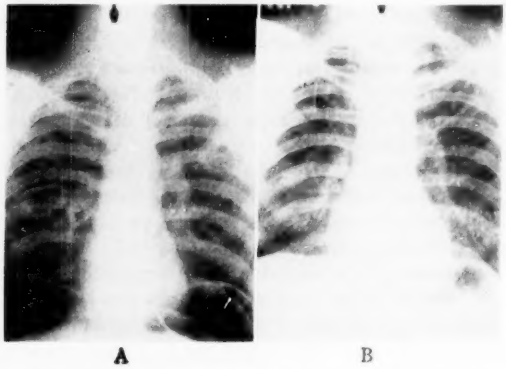


FIGURE 3. *Roentgenogram in G. L. before* (A) *and after Isoniazid Therapy* (B).

There was 1 patient (J. M.) with chronic schizophrenia who showed mental improvement on isoniazid while deteriorating physically. On isoniazid and streptomycin, he became bed ridden in spite of treatment. When he was bed ridden, with temperatures ranging from 101 to 102°F., he became quite talkative instead of being mute and withdrawn. One might conjecture that the mental change was due to toxicity in addition to the extra attention given him as a bed patient, rather than to the drugs he was receiving.

A patient who also had mental changes that did not fit into the pattern of improvement observed in the first 2 cases was admitted to Boston State Hospital for psychosis developing after a colostomy for tuberculous proctitis (he was in a remission of schizophrenic paranoid reaction before being started on isoniazid). He had been on isoniazid before he became psychotic, and until his remission no further isoniazid or streptomycin had been given, on the assumption that these drugs might have caused his psychosis. He was then placed on isoniazid again. During a two-month period of isoniazid therapy there was no return of his paranoid ideas, and he was returned for continued treatment to the hospital from which he had been referred.

Six patients in addition to those mentioned above showed mental changes, and these cases may be grouped together since the changes were similar and all were diagnosed chronic brain syndrome associated with alcoholic intoxication (Korsakow's psychosis). In all, there were 11 cases of alcoholic psychosis of the Korsakow type in the series. All showed slight to severe memory deficit, with complete inability to recall recent events and bizarre confabulations. Six of these 11 patients were originally very confused on admission, were started on isoniazid on admission and, along with improvement in tuberculosis, improved mentally during the course of treatment. This improvement consisted in lessening of confusion and lifting of apathy so that they became much more alert. All continue to show mild to severe memory deficit.

The improvement in mental status in these patients was not different from that seen in this type of psychosis when nutrition is improved. In fact, the 5 patients who did not show further improvement on isoniazid therapy had some weight gain and mental clearing that were due to good nutrition even before the isoniazid medication was begun. In all cases the x-ray films showed improvement, except for a patient who died of massive subcutaneous emphysema.

Another group of five patients received electroconvulsive therapy. Of these, 4 received five to twenty-five convulsive treatments; none of them showed any notable change. A fifth patient, who was started on isoniazid therapy on admission to the hospital, became a feeding problem a few days later. Frightened and withdrawn, as well as suddenly mute, he hid under his bed most of the day. As an emergency measure, one convulsive treatment resulted in his beginning to eat and talk again. Yet his mental status, as it appeared on admission, did not change essentially, and his psychosis could not be considered improved although the change mentioned appeared on isoniazid therapy. Significant changes in mental status are noted in Table 1.

Side Reactions

Most of the patients in this series were not communicative at all. All, in fact, being psychotic, had some aberrancy from what would be considered the normal in their communication with other people. Even those who talked were less communicative than might have been expected. Therefore, there were many who would not have mentioned subjective side effects even if they had been present.

There were no objective side effects during or after isoniazid medication.

Two patients who were talkative had subjective complaints. One complained of constipation, dizziness and headaches when her withdrawn, mute, catatonic behavior changed. She continued to complain of these effects in the hospital, but when last seen as an outpatient, she did not mention these complaints, although she was still receiving isoniazid.

Another patient complained of headaches and a rash on her forearms. (The rash was purely subjective; there were no visible signs of it.) She is being seen as an outpatient, having left the hospital, continues on isoniazid, and on her last visit she did not mention these complaints.

Mortality

Four deaths occurred during isoniazid therapy in cases that had been considered terminal at the start of treatment. One patient, a fifty-five-year-old woman, was severely depressed, with far-advanced pulmonary tuberculosis, Laënnec's cirrhosis and ascites. She died after twenty days on isoniazid therapy; the diagnoses were confirmed at autopsy. Another patient, a sixty-year-old man, had been treated for four years for pulmonary tuberculosis, receiving streptomycin and pneumoperitoneum unsuccessfully. Very moribund, he was started on isoniazid therapy. During the thirty subsequent days he showed an initial response, with increase in appetite and energy and lowering of fever, and then quickly failed. The third, a forty-year-old man, had pulmonary tuberculosis of twenty-five years' duration (orchiectomy for tuberculous orchitis had been performed twenty-five years previously), with periods of apparent arrest, and had been hospitalized for a chronic schizophrenic reaction, catatonic type, for fifteen years; he was moribund when isoniazid was begun and died fifteen days later.

A fourth patient, a fifty-one-year-old-man, died of subcutaneous and mediastinal emphysema after ten days of isoniazid therapy. He had been admitted to the hospital, four months before isoniazid was started, with far-advanced pulmonary tuberculosis and an alcoholic psychosis of the Korsakow type. Previously he had received streptomycin without improvement. His emphysema, a complication of pneumoperitoneum, began to develop two weeks before isoniazid treatment was begun. The diagnoses were confirmed at autopsy.

Summary and Conclusions

The observed effects of isoniazid on the tuberculosis process were not unlike those reported elsewhere as far as roentgenographic changes, appetite, weight, temperature, bacteriology and side effects are concerned. In some cases, isoniazid arrested the disease when streptomycin and collapse therapy had failed. In 21 cases in which initial improvement with isoniazid was not sustained, streptomycin was added to the program, with no clinical sign of drug resistance under the combined regimen.

Four patients with the diagnosis of acute brain syndrome associated with pulmonary tuberculosis showed remission of psychosis and also a slight improvement of the tuberculosis. Two patients improved slightly, without complete remission or arrest of pulmonary tuberculosis. In all these cases the psychosis developed after the pulmonary tuberculosis was discovered. In the patients who improved the psychosis was of comparatively short duration, apparently having been precipitated or aggravated by the pulmonary disease.

Of the other diagnostic categories, only the alcoholic patients showed mental improvement, and this was of the same type observed in the Korsakow psychosis when nutrition is improved, and could not be attributed to isoniazid. The other patients had no significant change in mental status while on isoniazid therapy.

Improvement in behavior and personality, to the prepsychotic level, was noted only in patients whose psychoses seemed to have been precipitated by the tuberculosis process.

Apparently, isoniazid is not a euphoriant and has no specific effect on mental status per se, affecting mental status only indirectly if mental or personality change has already been influenced by tuberculosis. If change or deterioration in mental status is attributed to toxic effects of tuberculosis, treatment with isoniazid can be expected to result in improvement in mental status paralleling the improvement of tuberculosis.

We are indebted to Mrs. Lillian O'Laughlin, R.N., and Mrs. Eugenia Green, for their assistance in the care of the patients.

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THE MECHANISM OF SYNCOPE ASSOCIATED WITH CHRONIC AURICULAR FIBRILLATION WITHOUT EVIDENCE OF ORGANIC HEART DISEASE*

Cure, after Ten Years, by Restoration of Sinus Rhythm with Quinidine

CHARLES K. FRIEDBERG, M.D.,† AND MORTON H. EDELMAN, M.D.‡

NEW YORK CITY

THE unusual opportunity of observing a patient with longstanding auricular fibrillation during an episode of syncope and of studying the possible mechanism responsible for the syncopal attack impels us to report the following case. Syncope or faintness is not unusual in patients with *paroxysmal* auricular fibrillation at the onset of the arrhythmia due to tachycardia or the sudden change in rhythm.[1-4] However, it is not a part of the clinical picture of established auricular fibrillation with relatively slow and unchanged ventricular rate in the patient with organic heart disease. Although syncope is often listed as one of the possible symptoms of chronic auricular fibrillation without evidence of organic heart disease,[5, 6] we have been unable to find any published record of observations made during the period of syncope that might explain its mechanism or of any electrocardiograms taken during the attack. We were able to observe one patient during a period of syncope sufficiently protracted to permit clinical and electrocardiographic studies.

The association of syncopal attacks with the arrhythmia presented not only the problem of mechanism but also that of the proper therapeutic management. Chronic auricular fibrillation is generally regarded as a serious and usually irreversible arrhythmia associated with advanced organic heart disease.[7] Except in cases due to hyperthyroidism, treatment is ordinarily directed against concomitant congestive heart failure or is designed to slow a rapid ventricular rate by the administration of digitalis. In more recent years there has been an increasing trend toward attempting to restore a regular sinus rhythm by means of quinidine, even in the presence of heart failure and embolization.[8, 9] The following case serves as a reminder that chronic auricular fibrillation does not always denote underlying advanced heart disease and that this arrhythmia may occur in the absence of any apparent cardiac or other organic heart disease.[2, 5, 6, 10, 11] It also demonstrates that regular sinus rhythm may be restored even after auricular fibrillation has persisted for many years.

CASE REPORT

A 35-year-old film producer had been told in 1942, when he was 26, that he had auricular fibrillation. He considered himself in good health at the time. In 1949, after a severe emotional strain, he had an attack of palpitation, which was controlled by sedation; since then he has been aware of palpitation after strenuous exertion or after a large meal. He experienced episodes of faintness and severe weakness on several occasions unrelated to any unusual activity or strain. Previous examinations had always revealed a heart of normal size and without cardiac murmurs. The basal metabolic rate in 1942 was −16 per cent. He had had no dyspnea, orthopnea, angina pectoris or edema. There was no history of rheumatic fever or diphtheria.

In March, 1950, he was treated at his home by one of us for acute maxillary sinusitis and viral pneumonia, which responded to penicillin and oxytetracycline therapy. During this illness auricular fibrillation was noted again, but no cardiac murmurs were detected, and the heart size was normal by fluoroscopy and radiography. The blood pressure was 120/70. At no time had he received digitalis or quinidine, nor had he been taking any medication immediately before the episode described below.

At 9 a.m. on March 12, 1951, he experienced a series of syncopal reactions, which became protracted and required hospitalization later that day. On the previous evening he had worked to a late hour and had been under more than usual strain. While descending in an elevator the next morning, he had 2 episodes of sudden severe weakness and faintness, breathlessness and palpitation. When brought to his physician's office, he was unable to sit up or stand. Syncope recurred when he tried to get up from the examining table, and he had to be hospitalized.

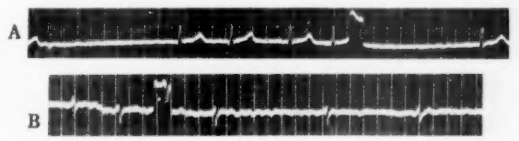

FIGURE 1. *Electrocardiogram Taken during the Initial Attack of Syncope.*

A = *Lead 1, with the patient in the recumbent position, showing auricular fibrillation with periods of ventricular asystole for 2 seconds and 2.2 seconds.*

B = *Lead 3, after intravenous administration of 0.8 mg. of atropine. Periods of ventricular asystole are slightly shortened.*

Physical examination revealed a tall, asthenic but well developed man who appeared acutely ill and manifested marked diaphoresis, cold clammy skin and great pallor. The heart rate was totally irregular, and the apical and radial pulses were 80 per minute, without a pulse deficit. The pulse volume was small. The blood pressure in the recumbent position was 85/54. When he sat up, the blood pressure fell rapidly, the pulse became weaker and finally imperceptible, and syncope recurred. He was given 3 minims of epinephrine by hypodermic as well as 60 mg. of phenobarbital and 20 mg. of Paredrine Hydrobromide by mouth. For 3 hours his condition was unchanged, and the blood pressure in the recumbent position remained between 80 and 90 systolic, falling precipitously when he tried to rise.

The heart appeared to be of normal size according to percussion and palpation of the apical impulse. The heart sounds were of normal quality. The cardiac rhythm was totally irregular, and there was an occasional long pause. Electrocardiograms taken during the initial syncopal attacks before admission showed auricular fibrillation, with periods of ventricular asystole of 2 seconds' duration (Fig. 1*A*). A tracing taken ½ hour after the intravenous administration of 0.8 mg. of atropine demonstrated a slight reduction in the duration of the periods of asystole (Fig. 1*B*). Carotid-sinus stimulation on both sides of the neck did not perceptibly alter the cardiac rate.

Examination of the blood revealed a hemoglobin of 13.5 gm. per 100 cc. and a white-cell count of 5300, with 70 per cent seg-

*From the Department of Medicine, Mount Sinai Hospital.

†Assistant clinical professor of medicine, College of Physicians and Surgeons, Columbia University; attending physician, Mt. Sinai Hospital.

‡Research assistant in microbiology, Mt. Sinai Hospital.

mented neutrophils and 30 per cent lymphocytes. The urine had a specific gravity of 1.018 and was negative for albumin and sugar; the sediment was normal. The stools were negative for occult blood. The erythrocyte sedimentation rate was 4 mm. per hour (Westergren method). The fasting blood sugar was 80 mg., and the serum cholesterol 320 mg. per 100 cc., and the plasma potassium 5.1 milliequiv. per liter. Radioiodine excretion after a tracer dose of I^{131} was 59 per cent (normal).

The findings on physical, electrocardiographic, x-ray and laboratory examinations were interpreted as excluding organic cardiac disease, hyperthyroidism, Addison's disease or any organic disease that might be responsible for syncope.

The patient was given 20 mg. of Paredrine Hydrobromide by mouth 3 times daily. The blood pressure on the 2d hospital day rose to 102/60. He recovered gradually and felt fairly well after an additional 24 hours. It was then decided to attempt to establish regular sinus rhythm. Accordingly, he received orally 0.4 gm. of quinidine sulfate every 2 hours for 5 doses. No effect on the cardiac rhythm was observed on the 1st day, although the pulse rate increased moderately. There was mild diarrhea, which was not disabling. On the next day he received 0.6 gm. of quini-

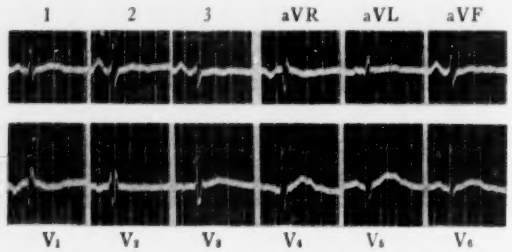

FIGURE 2. *Electrocardiograms on the Second Day of Treatment. Sinus rhythm was established after 3.2 gm. of quinidine in twenty-four hours. Prominent, wide P waves are seen in Leads 2, 3, aVR and aVF. The R-R' pattern is apparent in Leads V_1 to V_3. The T waves are broad and notched in Leads V_4 to V_6 and associated with U waves. Intra-auricular and intraventricular conduction defects are probably due to quinidine. Electrocardiograms subsequently became normal.*

dine sulfate every 2 hours for 5 doses. After the 2d dose of quinidine on the 2d day of treatment (after a total of 3.2 gm. of quinidine), the pulse became regular, and regular sinus rhythm was present, as demonstrated by electrocardiograms (Fig. 2).

Examination of the heart then revealed a regular rate of 66 beats per minute and no accentuated sounds or murmurs. On the 3d day of quinidine therapy 0.2 gm. of quinidine 3 times a day was begun as a maintenance dose. The patient left the hospital on March 21, in good condition. He was examined 10 days later and found to be normal, and the cardiac rhythm was still regular despite the fact that he had discontinued quinidine. An electrocardiogram was normal, and the rate was 65 beats per minute. At the time of last examination, 18 months after reversion to regular rhythm, the pulse was entirely regular and normal; during the interval he had had no further attacks of excessive weakness or syncope. He has noted occasional extrasystoles after heavy smoking or extreme nervousness. He has experienced occasional dull pain in the left upper anterior aspect of the chest followed by eructation. He has otherwise been in excellent health and spirits and has engaged in normal physical activity.

DISCUSSION

The essential abnormalities that could be related to syncope in this case were the periods of cardiac standstill, the mild hypotension during recumbency and the extreme hypotension when the patient was upright. Syncope, occurring at the onset of paroxysmal auricular fibrillation, has been related to hyperactive vagal reflexes resulting in cardiac standstill.[4] However, in the case reported above, the episode of syncope could not be attributed to the cardiac standstill both because the duration of the periods of standstill — namely, two seconds or less — was too brief to cause syncope and because the occurrence of syncope did not coincide with the periods of cardiac standstill. Furthermore, definite faintness or syncope did not occur when the patient was recumbent, despite the hypotension, presumably because the hypotension was not sufficiently severe. Syncope must therefore be attributed to postural hypotension, since it occurred only when the patient tried to assume the upright position, the blood pressure rapidly falling to minimal values and the pulse becoming imperceptible. The immediate cause of the syncope was the cerebral ischemia resulting from the maximal fall in blood pressure.

Since fainting due to postural hypotension may occur independently of cardiac disease or cardiac arrhythmia,[12] it is possible that the syncope in this case was unrelated to the auricular fibrillation. Although this possibility cannot be absolutely excluded, there are several indications that the syncope and postural hypotension were at least in part caused by the cardiac arrhythmia. It has already been stated that syncope has been repeatedly mentioned as one of the symptoms in cases of chronic auricular fibrillation without organic heart disease, although the presence of postural hypotension as the immediate mechanism has not been noted. The frequency of syncope appears to exceed by far that to be anticipated on the basis of accidental association. A causal relation between auricular fibrillation and syncope in this patient is suggested by the recurrent episodes so long as the auricular fibrillation was present and their absence for two years after the arrhythmia was abolished.

There are insufficient data to determine the mechanism by which auricular fibrillation may predispose to postural hypotension and consequent syncope. The association of bradycardia and brief periods of asystole with the postural hypotension and syncope suggests that the syncope should be attributed to a vasodepressor mechanism of the kind observed with the common faint or, less probably, with a hypersensitive carotid sinus.[13, 14] The occurrence of sweating, pallor and nausea in this case is also characteristic of the vasodepressor type of syncope. That the vasodepressor syncope in this case was not due to carotid-sinus hypersensitivity is indicated by the inability to induce cardiac standstill or vasodepression by manipulation of the carotid sinus, either during auricular fibrillation or after sinus rhythm had been established. That the syncope occurred in the presence of auricular fibrillation and disappeared when the rhythm was normal suggests that the heart with auricular fibrillation in some way sensitizes the neural arc responsible for the vasodepressor type of syncope. There is no collateral evidence to support this possibility or to explain such a mechanism.

Psychologic factors are commonly held responsible for vasodepressor syncope in normal subjects with normal cardiac rhythm. Hyperventilation from

psychogenic disturbance may act as the trigger mechanism that evokes the vasodepressor response in some cases.[15] The possible role of psychologic disturbance was therefore considered in this case for its possible relation both to the vasodepressor syncope and to the chronic auricular fibrillation without underlying organic heart disease. There is a reasonable basis for psychologic factors in this case, not only because of the patient's basic neurotic pattern but also because the syncopal episodes were most likely to occur during periods of unusual emotional strain. On the other hand, these psychologic factors are considered not to have been the sole cause for the syncopal attacks, which did not recur after regular cardiac rhythm was restored in spite of the fact that the basic neurosis and the emotional strains were apparently unaltered. One might assume that the syncopal syndrome was exclusively due to psychologic factors if one presupposed that the only effect of the fibrillating heart was to induce anxiety. Restoration of sinus rhythm would then be regarded as having abolished the vasodepressor reflex by eliminating anxiety over the cardiac abnormality.

It should be emphasized that the observations here reported refer to one episode of syncope in one patient. It is therefore possible that some other mechanism was responsible for other attacks in this patient or in other patients. However, we have been unable to find any record of blood pressure, pulse rate and electrocardiographic studies during an attack of syncope in a patient with chronic auricular fibrillation without evidence of organic heart disease. The possibility of some other causative mechanism is only conjectural at present.

It was decided to attempt to restore sinus rhythm not only because of the evidence of greater effectiveness of the heart when its rhythm is regular than when it is experiencing auricular fibrillation,[16-18] and the greater risk of heart failure[6, 19] and embolization[20] in the latter state, but also because this patient was repeatedly disturbed by palpitation and by episodes of weakness or faintness, as well as by actual syncope. His cardiac irregularity had been the cause of his rejection from the armed forces and for life insurance. He had avoided sports, including swimming, and many moderate activities for fear of damage to his heart. The sinus rhythm has thus far persisted for two years since its restoration, without maintenance doses of quinidine. During this period there have been no episodes of weakness, faintness or syncope, which were the actual complaints that led the patient to seek medical care.

Summary

A case of persistent auricular fibrillation for ten years, without evidence of organic heart disease, in a patient who experienced episodes of weakness, faintness or syncope is reported.

Observations, including electrocardiograms, made during a prolonged attack of recurrent syncope offer the first reported basis for explaining the mechanism of fainting in a case of chronic auricular fibrillation. Although there were brief periods of cardiac standstill and hypotension was present during recumbency, the episodes of syncope were actually due to postural hypotension and not to the standstill. Syncope could not be induced by carotid-sinus pressure.

The attacks of syncope are attributed directly to a vasodepressor reflex, but the mechanism and the neural pathway are uncertain. A causal relation between the auricular fibrillation and the syncopal attack is suggested by the occurrence of the latter only while auricular fibrillation persisted, but not after sinus rhythm was established. The findings in this episode of syncope and the suggested mechanism may or may not apply to other attacks in the same patient or in other patients.

Despite the ten-year duration of the auricular fibrillation, sinus rhythm was established in twenty-four hours by a total of 3.2 gm. of quinidine and has now persisted for two years without maintenance doses of quinidine.

Restoration of sinus rhythm has been followed thus far by elimination of the attacks of faintness and syncope.

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SPONTANEOUS RUPTURE OF THE NORMAL ESOPHAGUS*

RICHARD E. ALT, M.D.,† FRANK E. BIXBY, M.D.,‡ AND RUSSELL J. ROWELL, M.D.§

BEVERLY, MASSACHUSETTS

WITHIN a month during the past spring we had the unusual experience at the Beverly Hospital of caring for 2 patients with spontaneous rupture of the esophagus. Although this condition is not a medical curiosity, it is infrequent, and as a result, the clinical picture is not widely recognized. If this accident is undiagnosed and untreated, the result is invariably fatal. There are few other surgical emergencies in which early diagnosis and prompt treatment are so necessary to save life. The chief cause of death is delay, and the cause of delay is that esophageal rupture is not suspected. Yet when classic, the clinical picture may be so clear that the diagnosis may be made over the telephone.

CASE REPORTS

CASE 1. P. O., a 69-year-old retired man, was admitted to the hospital on March 23, 1953, for treatment of a chronic duodenal ulcer, which was causing intractable pain and occasional hematemesis. Ten years previously he had been operated on for perforated duodenal ulcer. Three months earlier he was in the hospital with similar symptoms, and a gastrectomy was advised but refused.

On this admission he was nauseated, had some dull pain in the epigastrium but was in no acute distress. Examination was not remarkable, and a chest film shortly after admission was normal except for healed tuberculosis of the right apex.

Four hours later he vomited undigested food and then complained of pain in the upper abdomen, which radiated to the mid-back. He was pale and restless. The respirations were 28, and the pulse 76, and the blood pressure fell from 120/76 on admission to 80/50. Pain was relieved by 75 mg. of Demerol; he slept in naps and did not seem profoundly ill, although the blood pressure remained below 100 during the night. On the following morning one surgeon thought that he might have a perforated ulcer and obtained a plain abdominal film, which showed no free air under the diaphragm. Whereas the upper abdomen was moderately rigid and tender, the lower abdomen was soft. The rapid, "catching" type of respiration, with pain limiting each inspiration, was striking. The patient was not in collapse, nor was his pain very severe.

Coronary thrombosis, dissecting thoracic aneurysm, acute pancreatitis and incarcerated diaphragmatic hernia were considered. The urinary diastase was normal, and an electrocardiogram showed no recent myocardial infarction.

An internist considered a coronary thrombosis unlikely, believing that the pathologic process was below the diaphragm, whereas the surgeon thought that it was above. In this case the surgeon was correct by about 1 cm. (This point is mentioned to emphasize the fact that rupture of the esophagus should be considered when localization above or below the diaphragmatic meridian is under question.) Later, the internist detected dullness at the left base and heard an unusual, evanescent clicking sound. Because of these findings, another chest film was taken, which showed fluid at both bases. Review of this film later showed mediastinal emphysema. Thoracentesis on the left produced gastric fluid. Since it was not certain whether the stomach had been inadvertently entered, the right pleural cavity was aspirated, and the diagnosis was made when similar fluid was obtained. Twenty-four hours had elapsed since the onset of symptoms because the diagnosis of perforation of the esophagus had not been considered earlier.

Under endotracheal anesthesia thoracotomy was performed, about 400 cc. of gastric fluid being aspirated from the left pleural cavity. The surfaces of the lung, diaphragm and mediastinum were covered by a gray exudate. The mediastinal pleura was completely disintegrated, and one could pass a finger readily through the mediastinum into the right pleural cavity; 1 cm. above the diaphragm there was a tear, 3 cm. in length, in the left lateral wall of the esophagus. The adjacent esophagus was normal. The mucosa was inverted and the esophagus was sutured with 5 No. 000 silk Lembert sutures. The pleural cavity was drained with an underwater seal. The patient's condition at the end of the operation was much improved. Culture showed beta-hemolytic streptococcus, and adequate antibiotic therapy was administered.

On the day after operation, the nonprotein nitrogen was 170 mg. per 100 cc., gradually rising to 230 mg. per 100 cc. A hydrothorax developed on the right and was aspirated. On the 6th day methylene blue, administered by mouth, was recovered from the pleural drainage. The patient died on the 8th postoperative day. Autopsy disclosed complete dissolution of the suture line in the esophagus and extensive mediastinitis.

In the entrance rotunda of Vanderbilt Hall, Harvard Medical School, a saying of Pasteur is inscribed in French for the edification of the medical students: "In the fields of observation chance favors those minds which are prepared." The truth of this maxim is well illustrated by the following case.

CASE 2. J. H., a 69-year-old retired man, was admitted to the hospital because of weakness, loss of weight and hoarseness, with a diagnosis of carcinoma of the stomach. In 1918 a gastroenterostomy had been performed for a duodenal ulcer, and he had had no symptoms until the present illness, which had begun 10 months previously.

Thirty hours after admission he vomited, and severe epigastric pain radiating to the back on the left then developed. The upper abdomen was tender; a diagnosis of perforated ulcer was considered by his physician. A surgical consultant found tenderness in the epigastrium and some rigidity. In addition, he observed crepitation in the neck.

The patient had difficulty in taking a deep breath, but there was no intense distress and no collapse. The blood pressure had fallen from 108/60 on admission to 98/60. The pulse was 54, and the respirations 24. A swallow of barium confirmed the diagnosis.

Under endotracheal anesthesia operation was carried out 6 hours after the onset of the severe pain. Thoracotomy was performed on the left. Pleural adhesions had walled off a pocket containing about 400 cc. of thin, cloudy, green fluid. This communicated with a tear in the esophagus, 3 cm. in length, immediately above the diaphragm on the left lateral wall. The adjacent esophagus was normal. The laceration was closed with 2 layers of Lembert sutures of No. 000 silk. The pleural cavity was drained with an underwater seal. A jejunostomy was performed.

The postoperative course was uneventful. One month later abdominal exploration was performed for carcinoma of the stomach. Unfortunately, the disease was so extensive that nothing could be done. This patient left the hospital a week later and is still fairly comfortable.

ETIOLOGY

The term "spontaneous rupture" is inaccurate. The condition under discussion was a complete tear in the lower esophagus precipitated by vomiting that occurred in patients who presumably had a normal esophagus immediately before the accident. The term "spontaneous" is used to distinguish this entity from other perforations caused by external

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†Surgeon-in-chief, Beverly Hospital.

‡Assistant in surgery, Beverly Hospital.

§Anesthesiologist, Beverly Hospital.

trauma, instrumentation, inlying tubes, missiles or perforation of ulcers. Although all are essentially traumatic, the evolution of the clinical picture is different in the latter. The same principles of early definitive repair apply to both groups.

It is well known that vomiting may cause injury to the esophagus. Vinson[1] reported cases of hyperemesis gravidarum in which mucosal rents developed that later healed, with stricture formation, and Weiss and Mallory[2] described mucosal lacerations just above the cardia in alcoholic patients caused by repeated retching and vomiting; these patients died of massive hematemesis. The authors were able to trace a sequence in 1 patient from a laceration to a chronic ulcer followed later by a complete rupture through the whole esophageal wall after vomiting. Although this rupture "in stages" may be the etiologic sequence in alcoholism, many patients with spontaneous rupture give no antecedent history of vomiting, hematemesis or alcoholism. It must be assumed that spontaneous rupture in most cases occurs through the whole esophageal wall with a single forceful insult to a previously normal esophagus.

Clinical Picture

The prompt recognition of this entity requires a knowledge of the physical events that follow the sudden rent in the lower esophagus, caused by forceful retching or vomiting, and an inclusion of this possibility in the differential diagnosis of problems of acute pain in the upper abdomen. In the classic picture, during or shortly after vomiting, the patient complains of severe pain in the upper abdomen and the anterior lower portion of the chest. Pain may be severe and may move to the back in the lower thoracic region and upward behind the sternum and into the shoulder; the pain is unremitting, causing breathing to be limited, and respirations may become short and rapid. The clinical signs of shock soon develop.

Within a few hours, the acid gastric juice digests the mediastinal pleura and spills over into one or both pleural cavities. The development of pleural effusions may be extensive and rapid. The patient observed a few hours after rupture is in acute distress. He is dyspneic, cyanotic and in peripheral vascular collapse. The upper abdominal wall may be rigid and tender, but the lower abdomen is soft. Because of the upper abdominal guarding and the rapid respirations, the surgeon is uncertain whether he is dealing with trouble above or below the diaphragm. When there is this clinical indecision whether the pathologic process is in the thorax or the abdomen, he should consider rupture of the esophagus as a possibility. Since the rupture usually occurs immediately above the diaphragm, the invariable combination of thoracic and abdominal symptoms and signs is readily understood.

Later, as the ectopic gastric juice continues to digest the mediastinal tissues, the surgeon (if he still carries a stethoscope) may be able to detect fluid at one or both bases, and he may occasionally hear a characteristic clicking sound that is due to air in the mediastinum. Or if he is very thorough and has a high index of suspicion, he may find subcutaneous emphysema in the neck or supraclavicular spaces. With a history of pain in the upper abdomen appearing after vomiting, the finding of subcutaneous emphysema in the neck is almost diagnostic of rupture of the esophagus. (It is not always present, however.)

The roentgenologist has occasionally made the diagnosis by discovering mediastinal emphysema on a film taken to determine the presence of air under the diaphragm. A film of the chest may also show hydrothorax, hydropneumothorax, mediastinal, cervical or supraclavicular emphysema. A conclusive diagnosis rests with the demonstration of a radiopaque fluid flowing through the opening in the esophagus into the mediastinum or pleural cavity.

Differential Diagnosis

When the three classic signs of rigid upper abdomen, dyspnea and subcutaneous emphysema are not present, when the subcutaneous emphysema has not been detected or when rupture of the esophagus is not considered, perforated peptic ulcer is most commonly the diagnosis. Many patients are first operated on abdominally because of an erroneous diagnosis of perforated peptic ulcer. Coronary thrombosis, pulmonary embolism, spontaneous pneumothorax, dissecting aneurysm of the thoracic aorta, acute pancreatitis, rupture of the diaphragm or incarceration of a diaphragmatic hernia, renal colic and acute cholecystitis have all been considered.

Surgical Treatment

After the diagnosis has been made, prompt action is necessary. For with the passing of each hour, corrosion of the mediastinum progresses, and infection of the mediastinal tissues sets in. Prompt resuscitative measures should be carried out before and while the diagnosis is being made to relieve the disastrous effect of prolonged hypotension. Prompt thoracotomy, under endotracheal anesthesia, with direct closure of the esophageal rent with two layers of interrupted fine-silk sutures, seems to offer the best hope of recovery. Our experience shows that thoracotomy with direct suture of the perforation can be performed with safety on critically ill, elderly, depleted patients in shock. The operation itself is one of the resuscitative measures.[3] The improvement in both cases reported above was striking after the mediastinum had been opened, the acid fluid removed, and the perforation sutured.

In patients who have survived the initial assault owing to smaller tears, less extensive digestion of

the mediastinum or localization of the fluid because of previous pleural adhesions, success has been achieved by closed drainage of the empyema. Appropriate antibiotic therapy, of course, should be instituted. A jejunostomy for feeding purposes at the time of the original operation was essential to recovery in Case 2. The continuation of Wangensteen suction with a Levin tube in the stomach through the esophagus is essential in the prevention of postoperative vomiting.

Summary and Conclusions

The clinical picture of sudden rupture of the esophagus caused by vomiting is characterized by rigidity and tenderness of the upper abdomen, difficulty in breathing, subcutaneous emphysema and shock. The diagnosis of rupture of the esophagus should be considered when there is uncertainty whether the pathologic process is above or below the diaphragm in patients presenting acute upper abdominal pain.

Once suspected, the diagnosis can be confirmed by the finding of mediastinal emphysema on a chest film, gastric fluid on thoracentesis or an opening in the esophagus after a barium swallow.

Delay is fatal. Prompt resuscitative measures followed by thoracotomy under endotracheal anesthesia, with primary suture of the esophageal tear, is the procedure of choice.

Two cases in elderly patients are reported. In 1 case primary suture was performed twenty-four hours after the rupture, and the patient survived for eight days. Death was due to mediastinitis and dissolution of the esophageal suture line. In the other case primary suture was performed six hours after rupture, and the patient recovered rapidly; later, he was found to have inoperable carcinoma of the stomach.

If the patient is not moribund and good anesthesia service is available, prompt primary suture of the esophageal tear offers the best chance of recovery.

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MEDICAL PROGRESS

LIVER BIOPSY (Concluded). II. THE RISK OF NEEDLE BIOPSY*

Norman Zamcheck, M.D.,† and Oscar Klausenstock, M.D.‡

BOSTON

Complications of Liver Biopsy

Most needle biopsies are free of complications. Klatskin[194] reported that more than 80 per cent of 352 needle biopsies were without mishap (Table 1). Terry,[195] reviewing 7532 biopsies noted 24 "significant" complications, an incidence of only 0.23 per cent.

Pain, the most frequent complication of liver biopsy, variously reported in 5 to 50 per cent of patients,[6] is usually short lasting and may be controlled readily by routine analgesics.[196] Perhaps, the best indication of this is the willingness of almost all patients to permit repeat biopsy. Multiple biopsies have been performed on many patients, as many as 6 within four weeks on 1[39] and 13 on another.[136] A confident, reassuring manner, a simple explanation of the procedure and careful application of local anesthesia minimize preoperative apprehension and subsequent pain.

A brief friction rub caused by fibrinous perihepatitis or pleuritis is occasionally heard over the liver after biopsy.[19] Pleural hemorrhage, effusion and pneumothorax may follow the transdiaphragmatic route. We have observed transfer of ascitic fluid through a perforated right leaf of the diaphragm into the thorax in 3 cases with mild respiratory embarrassment. Boucher et al.[197] reported pleural bile effusion in a patient with obstructive jaundice. Avoidance of the upper margin of the intercostal space minimizes the danger of perforation of an intercostal vessel. Despite the frequently asserted danger of perforating large diaphragmatic veins, no hemorrhages from this source have been reported.§

Penetration of abdominal viscera other than the liver or gall bladder is a rare complication of needle biopsy. Terry[195] found no report of this complication in reviewing 7532 needle biopsies performed since 1939. Baron[1] biopsied the colon without consequence. One alleged fatal case after accidental puncture of the colon was brought to the attention of Hoffbauer,[5] but no detailed description of this

*From the Department of Medicine, Harvard Medical School, the Second and Fourth Medical Services (Harvard), Boston City Hospital, the Mallory Institute of Pathology, Boston City Hospital, and the Department of Pathology, Boston University School of Medicine.

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†Instructor in medicine, Harvard Medical School; research pathologist, Mallory Institute of Pathology; research associate in pathology, Boston University School of Medicine; formerly, Senior Damon Runyon Clinical Research Fellow.

‡Intern in medicine, Fifth and Sixth Medical Services (Boston University), Boston City Hospital.

§A case with alleged bleeding from a diaphragmatic vessel has recently come to our attention. The patient died 18 hours after transthoracic biopsy, and the liver at autopsy contained both miliary tubercles and metastatic cancer. The fact that 1000 cc. of blood was found in the abdominal cavity and none in the pleural space raises some doubt about the diaphragm as the source of bleeding, however.

case has been found. Reynolds[198] refers to a similar case in which colonic mucosa was obtained on biopsy. There was no evidence of peritonitis or untoward sequelae, however, and laparotomy three days later revealed no site of puncture.

Perforation of the distended gall bladder[2, 22, 199] is also rare. Kleitsch and Kehne[200] believe that it results only from the unwarranted use of the abdominal approach to a liver that is either not palpable or only slightly palpable. Most workers are now agreed that this danger of the transabdominal approach to the liver precludes its routine use.

TABLE 1. *Complications Encountered in 352 Liver Biopsies.**

COMPLICATION	NO. OF PATIENTS	PERCENTAGE
None	291	82.6
Pain requiring analgesics	45	13.0
Fall in blood pressure	5	1.4
Low blood pressure requiring transfusions	3	0.8
Fever	3	0.8
Bleeding at biopsy site	3	0.8
Probable bile peritonitis†	1	0.3
Pleural effusion	1	0.3

*Based on data of Klatskin.[104]
†Surgical intervention not required.

Bile peritonitis, a serious complication of liver biopsy, results almost entirely from bile leakage from the dilated biliary passages of patients with obstructive jaundice.[199] Terry reported 11 cases of biliary peritonitis, 3 requiring laparotomy. Obstructive jaundice existed in 10 of these and had recently been present in the other.[198] Because of the hazard of this complication, biopsy is usually contraindicated in patients with known obstructive jaundice. Bile peritonitis from nonobstructive jaundice has not been reported. Neither Sherlock[9] nor Weisbrod[107] mentioned this complication in a total of 338 biopsies on jaundiced patients. Accordingly, clinical findings consistent with bile peritonitis occurring promptly after needle biopsy in jaundiced patients is prima-facie evidence of obstructive jaundice, and early laparotomy should be considered. Prompt decompression of the biliary passages is indicated.

Brown and Walsh[201] reported a fatal outcome in a markedly jaundiced patient after liver biopsy done in an attempt to distinguish between obstructive and intrahepatic disease. At autopsy, golden-brown pigment masses were found in many of the arteries of both lungs. These were interpreted by the authors as bile emboli. The entire biliary system was dilated. There was no microscopical evidence of primary liver disease.

Hemorrhage from the liver is the most frequent serious complication and the chief cause of death. Bleeding after biopsy has been observed to consist usually of a thin trickle from the puncture wound in the liver lasting ten to sixty seconds and totaling 5 to 10 cc.[68] Most cases of fatal hemorrhage have resulted from perforations of distended portal or hepatic veins or aberrant arteries (Table 2). In some cases a tear of the liver occurred when a patient breathed deeply during intercostal biopsy. The bleeding tendency and impaired blood coagula-

TABLE 2. *Causes of Death in 39 Cases after Liver Biopsy.*

CASE NO.	AUTHOR	YEAR	CAUSE OF DEATH	CLINICAL & AUTOPSY FINDINGS	UNDERLYING DISEASE OF LIVER	COMMENT
1	Bingel[109]	1923*	Hemorrhage	Autopsy diagnosis, cancer of stomach, with extensive replacement of both adrenal glands by tumor and hemorrhagic infarction of remainder of adrenal glands	Not reported	No coagulation studies done; slow biopsy technic, now discarded; ? role of adrenal insufficiency in death.
2			Hemorrhage	Severe pernicious anemia (red-cell count, 500,000); patient breathed during intercostal insertion of needle.	Not reported	No coagulation studies; slow procedure used.
3	Olivet[108]	1926	Hemorrhage	Clinical & autopsy diagnosis, carcinoma of pylorus, with extensive metastases to liver, lymph nodes & adrenal glands (blood in peritoneal cavity did not coagulate on standing).	Metastatic carcinoma of liver	Death 2 hr. after biopsy; no prothrombin time determined before biopsy; author believes this to have been prolonged.
4			Hemorrhage	Clinical diagnosis, ? chronic lead poisoning and pernicious anemia (red-cell count, 575,000); autopsy revealed hemorrhage into peritoneal cavity.	Hemosiderosis	Patient in very poor condition; no transfusions given; no coagulation studies performed before biopsy in spite of patient's severe anemia; biopsy done through intercostal route and patient breathed during procedure, which resulted in tear of liver capsule; death 24 hr. later.
5			Peritonitis	Clinical diagnosis, hepatomegaly, undetermined cause; autopsy diagnosis, carcinoma of gall bladder, with extensive metastases to liver, subphrenic abscess and early peritonitis.	Metastatic carcinoma of liver, with subphrenic abscess	Signs of peritonitis soon after biopsy; patient died 36 hr. later; although not demonstrated, assumed that needle biopsy caused extension of infection from abscess to peritoneum; no chemotherapy available.
6	Toullec & Huard[204]	1935	Hemorrhage	No information	?	No evaluation possible.
7	Baron[1]	1939	Hemorrhage	Autopsy showed exsanguinating hemorrhage from 1-cm. tear in liver	Extensive metastatic carcinoma of liver	No coagulation studies done; patient breathed during procedure (abdominal route).
8	Kofler[205]	1940	Hemorrhage	No information	?	No evaluation possible
9			Hemorrhage	No information	?	No evaluation possible

*The year given does not usually correspond to the actual year of death, which in most cases occurred one or more years previously. It corresponds either to the date of the report or to that when information was obtained for the purpose of this review.

TABLE 2 (*Continued*).

CASE NO.	AUTHOR	YEAR	CAUSE OF DEATH	CLINICAL & AUTOPSY FINDINGS	UNDERLYING DISEASE OF LIVER	COMMENT
10	Roholm et al.[246]	1942	Hemorrhage	Clinical diagnosis, progressive jaundice; autopsy showed bleeding into peritoneal cavity	Carcinoma of head of pancreas, with obstructive jaundice	Operator admitted prothrombin activity not tested before biopsy, but later found to be very low; death 9 days after biopsy, with general signs of hemorrhagic diathesis.
11			Hemorrhage	Clinical diagnosis, long-standing jaundice; autopsy showed intraperitoneal hemorrhage	Metastatic carcinoma of hepatoduodenal ligament, primary, unknown	In spite of prolonged prothrombin time, vitamin K not administered before procedure, by oversight; death 10 hr. after biopsy.
12	Raby[247]	1944	Hemorrhage	Clinical diagnosis, jaundice of obscure origin	?	Death precipitated by biopsy (needle punctured superficial branch of portal vein); 1.5 liters of blood in peritoneal cavity (clotting time had been normal).
13			Unknown	No information	?	Death 3 days after biopsy; no proof that death caused by biopsy; no cause of death found at autopsy.
14	Davis[248]	1947	? Hemorrhage	Autopsy diagnosis, severe hepatic damage, with bile nephrosis	?	Pathologist's opinion that cause of death hepatic and renal failure rather than hemorrhage; patient not in shock and lost only 500 cc. of blood.
15	Buck[48]	1948	Hemorrhage	Clinical diagnosis, acute liver failure.	Widespread necrosis & hepatitis superimposed on fatty cirrhosis	Patient critically ill; death 3 hr. after 2d (interval) puncture, performed on unco-operative patient; marginal prothrombin time (50 per cent).
16	Griesemann[249]	1949	Hemorrhage	Autopsy showed injury to branch of portal vein without any tear of liver; 1.5 liters of blood in peritoneal cavity.	Long-standing subacute catarrhal icterus	Death unquestionably precipitated by biopsy
17	Hoffman & Rosenthal[58]	1950	Bile peritonitis	Autopsy showed bile peritonitis apparently caused by needle's entering obstructed & dilated intrahepatic biliary duct, producing oozing and bile peritonitis	Apparently obstructive jaundice	Death 3 days after biopsy, which operator considered cause of death; no clinical or laboratory data given.
18	Gallison & Skinner[199]	1950	Bile peritonitis	Clinical diagnosis, jaundice & alcoholism (equivocal laboratory tests); autopsy showed 8000 cc. of turbid, dark-yellow, watery fluid in peritoneal cavity.	Post-mortem findings included adenocarcinoma, Grade 2, of ampulla of Vater, with obstruction of common bile duct, pancreatic necrosis, slight, & portal and biliary cirrhosis	Death 7 days after & clearly related to biopsy
19	Moyer & Wurl[180]	1951	? Hemorrhage	No bleeding point found at laparotomy or autopsy	Fatty metamorphosis, with passive congestion	History of repeated gastrointestinal hemorrhage; intraabdominal bleeding developed; death 4 days after biopsy, which was not directly responsible; immediate cause of death, during laparotomy, considered "cardiac arrest" secondary to severe coronary-artery disease.
20	White (cited by Terry[186])	1951	Hemorrhage	None available	Advanced cirrhosis of liver	Low prothrombin time
21	Sherlock[219]	1952	Hemorrhage	Both patients moribund, with severe liver disease; 1 also had general paresis & rectal cancer.	One had acute & other subacute necrosis of liver	Patients already moribund; large-bore needle then used (now discarded).
22			Hemorrhage			
23	Gillman[251]	1952	Hemorrhage	Autopsy showed unusual artery in liver had been punctured (peritoneal cavity filled with blood)	Tuberculous hepatosplenomegaly	Patient suddenly collapsed 2 hr. after puncture, with signs of intraperitoneal hemorrhage; death unquestionably precipitated by biopsy.
24			Hemorrhage		Widespread hepatic carcinoma	Patient moribund at time of biopsy
25	Volwiler & Jones[18] & Ellis[252](Massachusetts General Hospital)	1952	Hemorrhage	Autopsy showed large laceration extending entire length of rt. lobe (needle had pierced rt. main hepatic vein, leading to intrahepatic bleeding & splitting friable amyloid liver)	Amyloid disease	Severe abdominal pain; shock 10 hr. after biopsy which undoubtedly precipitated death; prothrombin time borderline (prolonged 6 sec.)
26			Peritonitis	Autopsy showed peritonitis (due to beta-hemolytic streptococcus), with septicemia.	Fulminating acute cirrhosis	Operators did not believe biopsy, performed 5 days before death, was cause of peritonitis; temperature chart gave no clue to time of onset of peritonitis.

TABLE 2 (*Concluded*).

Case No.	Author	Year	Cause of Death	Clinical & Autopsy Findings	Underlying Disease of Liver	Comment
27			Bile peritonitis	Autopsy showed obstruction of common bile duct by carcinoma	Obstructive jaundice	Death clearly related to biopsy
28			Hemorrhage	Autopsy showed large vein perforated, with 1500 cc. of blood in abdominal cavity	Oat-cell carcinoma, with metastases to liver	Patient went into shock; death clearly related to biopsy.
29	Klatskin[113]	1952	Hemorrhage	Autopsy showed large vein punctured by needle	Widespread lymphoma	Biopsy clearly cause of hemorrhage
30			? Hemorrhage; ? neurogenic shock.	Autopsy showed 2 1-cm. lacerations approximately 2 cm. in depth	Moderately severe hepatitis	Operator did not believe that shock was due to blood loss alone; patient given total of 3 liters of blood immediately & yet peritoneal cavity contained only 400 cc. of blood; death 3 hr., 25 min., after biopsy; patient took deep breath while specimen was being obtained & lacerations believed to have occurred at that time; ? neurogenic shock.
31	Rubenstone et al.[114]	1952	Bile peritonitis	Clinical diagnosis, obstructive jaundice; autopsy showed obstruction of common bile duct by precipitated putty-like material (cholangiectatic duct had been accidentally transversed).	Obstructive jaundice	Death 4 days after & clearly related to biopsy; 2000 cc. of bile-stained fluid in peritoneal cavity; culture showed *Escherichia coli* & *Bacillus subtilis*.
32	Armed Forces Institute of Pathology[115]	1952	Hemorrhage	Clinical diagnosis, carcinoma of hepatic flexure of colon (needle biopsy showed adenocarcinoma); autopsy revealed adenocarcinoma of head of pancreas, with metastases to liver.	Metastatic carcinoma	Patient went into shock & died from hemorrhage at site of biopsy, which probably precipitated death.
33			Hemorrhage	Clinical diagnosis of tuberculosis of spine & liver disease; autopsy showed tuberculosis of spine & amyloidosis of liver, kidney & spleen.	Amyloid disease (no amyloid found in section of liver from which biopsy was taken)	Death from hemorrhage 10 hr. after biopsy, which was considered cause of death
34	Brown & Walsh[116]	1952	? Bile embolism; ? neurogenic shock.	Clinical & laboratory findings not reported (bile aspirated with syringe during biopsy); autopsy showed severe obstructive jaundice, with greatly dilated gall bladder & biliary system, caused by carcinoma of ampulla of Vater; lung capillaries reported to contain bile; no hemorrhage found.	Bile stasis	Patient went into circulatory collapse &, despite transfusions, died 7 hr. after biopsy, which was undoubtedly related to death; mechanism obscure. Although case reported as fatal bile embolism, no mention of respiratory distress; impossible to evaluate case further because of paucity of clinical & absence of laboratory data.
35	Boston City Hospital[118]	1952	Hemorrhage	Autopsy showed liver laceration	Laënnec's cirrhosis	Biopsy precipitated death in hopelessly ill patient, who was in terminal coma & breathed during procedure; low prothrombin time.
36			? Hemorrhage	Clinical diagnosis, widespread metastatic cancer of liver; no autopsy performed.	Metastatic cancer of liver	Biopsy contributed to death; low prothrombin time (40 per cent).
37	Welin[119]	1952	Peritonitis, purulent	Clinical diagnosis, icterus of several months' duration, with anemia & intestinal bleeding; autopsy showed carcinoma of bile ducts, with dilatation of biliary passages, subphrenic abscess & diffuse peritonitis.	Carcinoma of bile ducts	"At biopsy, infectious material apparently had been carried to the peritoneal cavity through puncture of a dilated bile duct"; (patient went into shock but recovered); several days later ileus developed, followed by death.
38	Rumball[117]	1952	? Hemorrhage; ? neurogenic shock.	Clinical diagnosis, extrahepatic biliary obstruction, with intense jaundice; autopsy showed 200 cc. of clotted blood over dome of liver & 250 cc. in pelvis.	Carcinoma of pancreas	Four hr. after biopsy patient went into shock & died shortly afterward; death apparently related to biopsy; operator believed that "actual amount of blood loss was insufficient to cause death; and although several theories have been advanced, no adequate explanation is apparent."
39	Marshall[111]	1952	Hemorrhage	Autopsy diagnosis, reticulum-cell sarcoma, with marked icterus, prothrombin time 65 per cent; autopsy showed 5000 cc. of blood in peritoneal cavity.	Reticulum-cell sarcoma	Three attempts made to obtain liver sample; 1 hr. after biopsy patient complained of abdominal pressure & desire to defecate; in spite of 2500 cc. of blood patient died 6 hr. after biopsy; death clearly related to biopsy; needle punctured 0.8-cm. vein situated 2 cm. below surface of liver.

tion associated with severe liver disease undoubtedly enhance the danger of severe bleeding.[219] Significant hemorrhage occurred 16 times, or 0.2 per cent, in 7532 biopsies.[195] Laparotomy was required in 4 patients, transfusion alone in 3, and expectant treatment in 9.

Kleckner et al.[220] reported 2 cases of transient "pleural shock" lasting one or two hours after biopsy. Inexplicable fatal shock has been described[213, 217] in at least 2 cases (Table 2): 1 patient, a sixty-seven-year-old man with severe homologous serum hepatitis,[213] was biopsied by a resident who had done at least 100 biopsies. The patient breathed deeply just as the specimen was being obtained through the ribs. Fifteen minutes later he went into shock. Transfusion was started immediately, and within half an hour an intra-arterial cannula was inserted, and a large volume of blood transfused under pressure. Despite the administration of 3 liters of blood, the blood pressure did not rise above 60 systolic, and the patient died three hours and twenty-five minutes after the biopsy. At autopsy, two 1-cm. lacerations, approximately 2 cm. in depth, were found in the liver. Surprisingly enough, the peritoneal cavity contained only 1 liter of liquid blood and 400 cc. of clotted blood (this volume of blood had been replaced within half an hour of the onset of bleeding). Nevertheless, the patient remained in shock and did not regain consciousness. In these cases the irreversible shock could not be explained on the basis of blood loss alone.

Implantation of tumor cells in the needle track has been reported.[221, 222] No case of air embolus has been reported although the theoretical possibility has been mentioned.[5]

TABLE 3. *Fatal Cases among 20,016 Needle Biopsies of the Liver.*

AUTHOR	YEAR OF REPORT	NO. OF BIOPSIES	ALLEGED FATAL CASES
Schupfer[205]	1907	40	0
Binger[206]	1923	100	2
Olivet[207]	1926	140	3
Waldenström[210]	1928	39	0
Toullec[186]	1935	163	1
Frola[208]	1935	66	0
Baron[1]	1939	48	1
Kofler[216]	1940	100	2
Roholm[196]	1942	297	2
Buck[49]	1948	56	1
Cogswell[19]	1949	403	0
Griessmann[209]	1949	32	1
Hoffbauer*	1949	400	0
Hoffman[89]	1950	43	1
Haex*	1950	1500	0
Ricketts*	1950	300	0
Caravati*	1950	300	0
Moyer[188]	1951	200	1
White*	1951	761	1
Davis*	1951	500	1
Ellis[211] (including Volwiler and Jones)	1952	750+	4
Sherlock[218]	1952	650	2
Molle[47]	1952	401	0
Schiff[204]	1952	1349	0
Klatskin[212]	1952	1054	2
Armed Forces Institute of Pathology[215]	1952	2000+	2
Gilliman[211]	1952	1828‡	2
Boston City Hospital[214]	1952	400	2
Welin[240]	1952	400	1
Rumba[217]	1952	308	1
Marshall[216]	1952	655	1
Totals		15,274	34†
Additional series without fatal outcome [169-173, 178-198] including others [60, 140, 160, 201-240] collected by Terry[195]		4,742	
Total		20,016	

*Reported in Terry's[195] series.

†In addition to these, reports of 5 cases are available but were not included because the authors failed to indicate the total numbers of biopsies performed (see Table 2).

‡Excluding 454 biopsies on baboons and other animals.

Mortality

The wide acceptance of needle biopsy throughout the world is due largely to its low mortality in qualified hands, which Sherlock,[221] in 1949, estimated to be 0.29 per cent in 3159 patients, and Gallison and Skinner,[199] in 1950, to be 0.35 per cent in 4911 cases. Omitting fatal cases occurring before 1939, Terry[195] calculated the mortality in 1952 to be only 0.12 per cent in 10,600 cases. Reviewing 20,016 needle biopsies since 1907 we found 34 alleged deaths, making a mortality of 0.17 per cent (Table 3). Five authors reported additional fatal cases without indicating the total number of biopsies performed. If these cases are included a maximum mortality of 0.194 per cent is obtained. Each case is summarized in Table 2. We are aware of the possibility of error in reviewing published case histories. Yet this is essential to indicate the true mortality of needle biopsy. Much has been learned in the past fifteen years since needle biopsy was reintroduced by Iversen and Roholm.[6] There has been a steady improvement in methods and in criteria for selection of patients. Thus, outmoded procedures for biopsy were used in some early cases. At least 7 of the fatal cases occurred before 1940, when tests for liver function and blood coagulation were less reliable. Facilities for blood transfusion were sometimes limited, and antibiotics unavailable. The frequency of bleeding tendencies in patients with severe liver disease[219, 224, 225] has only recently been re-emphasized. Fatal biopsy was performed on 9 patients who would now be considered relatively poor risks; 4 of these were moribund at the time of biopsy. Coagulation was known to be defective in 4 others, and 1 patient was clearly unco-operative. Re-evaluation of 3 other fatal cases was impossible because of insufficient or unavailable data. Of the

TABLE 4. *Re-evaluation of Reported "Fatal" Cases after Needle Biopsy of Liver.*

CAUSE OF DEATH	TOTAL NO. OF PATIENTS	FATALITIES ACCEPTABLE UNDER CURRENT CRITERIA		
		YES	NO	?
1. Hemorrhage	25	9	16	
2. ? Hemorrhage	5	2*	2	1†
3. Bile peritonitis	4	4		
4. Suppurative peritonitis	3	1	2	
5. ? Bile embolism	1	1*		
6. Unknown	1			1
Totals	39	17	20	2

*? Neurogenic shock.

†Cardiac arrest.

39 fatalities (Tables 4 and 5) only 17 appeared acceptable when considered in the light of present knowledge. Excluding these cases the true mortality of 0.085 per cent is obtained (Table 6).

The large series reported by several of the most experienced authors confirm the fact that a mortality approaching zero is indeed possible. Thus,

TABLE 5. *Re-evaluation of 39 Fatal Cases Attributed to Needle Biopsy.*

REASON FOR EXCLUSION		No. OF CASES
Fatal case before 1940		7
Death clearly unrelated to biopsy		3
Biopsy contraindicated		9
Patient moribund	4	
Coagulation defective	4	
Unco-operative patient	1	
Evaluation impossible because of insufficient data		3
Fatal classification acceptable under current criteria		17
Total		39

Schiff[226] and his associates performed more than 1300 biopsies, and Haex[227] more than 1500 without a death. The experience observed at the Boston City Hospital is typical of that in many institutions. In 1945 needle biopsy was first introduced into the Harvard Clinical Unit. Two deaths occurred among

TABLE 6. *Adjusted Mortality in 20,016 Needle Biopsies of the Liver.*

CLASSIFICATION	No. OF CASES	PERCENTAGE
Gross mortality:		
Deaths occurring in reported series	34	0.170
5 additional isolated cases	39	0.194
Adjusted mortality:		
Deaths acceptable under current criteria	17	0.085

the first few biopsies performed. Both patients were terminally ill, 1 in hepatic coma and the other with widespread cancer. In retrospect, it is clear that the procedure was unduly risky in both patients. Since that time almost 500 biopsies have been performed by 4 members of this clinic without serious

TABLE 7. *Underlying Disease in 17 Cases Accepted As Fatalities.*

DISEASE	No. OF CASES
Obstructive jaundice	2
Carcinoma of ampulla of Vater	2
Carcinoma of common bile duct	2
Metastatic carcinoma of liver	2
Widespread lymphoma	2
Hepatitis	2
Amyloid liver	2
Carcinoma of pancreas	1
Tuberculosis of liver	1
Unknown	1
Total	17

complication.[216] No patient has required transfusion or laparotomy after biopsy.

Fatal complications occurred most commonly in patients gravely or hopelessly ill at the time of biopsy (Table 7). Nine of the 17 cases apparently acceptable as fatal were associated with carcinoma, 2 with amyloid disease, 2 with severe hepatitis and 1 with tuberculosis of the liver. Thus, it is apparent that even with the most discriminate use, a premature death may be precipitated by biopsy in patients with markedly depleted reserve.

There is abundant evidence that the frequency of serious complications, including death, is high in inexperienced hands. Unreported fatal cases are known to have occurred at the hands of inadequately trained personnel. Although needle biopsy is a relatively simple procedure to perform, it should not be undertaken casually. There is general agreement that its use should be reserved for those familiar with liver disease, and that training should be acquired under their supervision. The failure to appreciate these facts has sometimes led to disaster and has unduly prejudiced some clinics against the use of the method.

In the past the use of needle biopsy has often been limited by fear of its complications. It is now apparent that the most conservative application of the method results in a mortality approaching that of other accepted procedures, such as spinal puncture and anesthesia, abdominal and pleural paracentesis[215] and gastroscopy.[216] Additional study is necessary before one further defines the group of marginal-risk patients in whom the hazard of management without benefit of biopsy diagnosis may exceed the risk of biopsy itself.

PRECAUTIONS AND CONTRAINDICATIONS

The proper selection of patients as candidates for biopsy entails balancing the potential diagnostic value of the procedure against its possible risk to the patient. The following precautions and contraindications have proved useful in reducing this risk:

First of all is the importance of training and experience, which was emphasized above. The occasional performance of needle biopsy is not likely to give operators confidence. Since assurance of manner is essential for complete patient co-operation, a manifest lack of confidence increases the danger of the procedure.

Secondly, the patient must be co-operative and able to carry out simple instructions involving control of respiration, especially when the transpleural approach to the liver is utilized. He is advised that he may experience some pain, most or all of which can be eliminated during the procedure by local anesthesia. Sedation may be given routinely to patients who are not in impending liver failure: 50 to 75 mg. of Demerol injected ten to twenty minutes before biopsy has been found satisfactory in this clinic.

Thirdly, although some workers recommend routine typing and cross-matching of blood for all patients, it is the practice of others to reserve this precaution for the more seriously ill patients.

Parenteral administration of vitamin K may be given prophylactically when necessary before the performance of the procedure.

Fourthly, the size and position of the liver vary from person to person and must be defined by percussion, palpation and, when necessary, x-ray examination. When the exact location is obscured by masses, fluid or operative scars, it is unwise to proceed. Although ascites in small amounts may not hamper the procedure, large quantities should be removed before biopsy. The physician must always have a clear awareness of the relation of the point of his needle to the liver. Hit-or-miss insertion of the needle is never justified, and clearly admits confusion. The percussion flatness of unexpected pleural or subdiaphragmatic fluid is sometimes mistaken for that of the liver, with consequent malpositioning of the biopsy needle.

Fifthly, to make correct decisions about the use and timing of needle biopsy familiarity with clinical liver disease in its many ramifications is imperative. The procedure itself may occasionally have to be altered during performance. For example, failure to meet the firm resistance of an anticipated cirrhotic liver may suggest reposition of the needle to the experienced operator, but may invite the neophyte to hazardous deeper insertion. Similarly, a soft, fatty or necrotic liver may offer so little resistance that it may induce the unsuspecting physician to make an unnecessarily deep penetration. Failure to meet liver resistance may confirm the clinical suspicion of a shrunken liver.

Sixthly, chronic passive congestion of the liver has been considered by some as a relative contraindication.[47] Sherlock,[27] however, has performed biopsies on 50 patients with chronic passive congestion without complication.

Seventhly, the presence of suppuration in the areas of approach to the liver contraindicates needle biopsy. Whenever we have unexpectedly encountered accumulations of pus in the pleural or subdiaphragmatic spaces, efforts to pierce the liver at that site have been discontinued. Because of the diagnostic importance of such unexpected findings, a sterile tube is included in the routine kit for collection of pus.

Eighthly, the small or nonpalpable liver may be difficult to biopsy, and a few workers[47] consider this a contraindication. We do not share this view.

Ninthly, enthusiasm for the use of liver biopsy has introduced the danger that it may be considered a substitute for complete clinical and laboratory work-up. This is clearly unwarranted.[67] The procedure should not be used until study by usual methods has been completed.

Tenthly, since the risk of biopsy is increased in the presence of jaundice, the selection of such patients is particularly important. Needle-biopsy confirmation of obvious extrahepatic obstructive jaundice is unwarranted. Sherlock[210] tends to avoid biopsy in the presence of deep jaundice, and Molle[47] is reluctant to biopsy any jaundiced patient. The decision in a given case of jaundice must be made on an individual basis. Most workers agree that the advantages accruing to the jaundiced patient far outweigh the risk.

Eleventhly, in general, liver biopsy is contraindicated in patients manifesting bleeding tendency or impaired blood coagulation. Most workers require a prothrombin time of 50 per cent or better before performing needle biopsy. Although this value was arbitrarily established, it has proved generally reliable. It may not guarantee freedom from bleeding in all cases, however. Because of the known vagaries of the one-stage prothrombin determination, the usual method for determining prothrombin time, we are prone to disregard a normal prothrombin time when there is evidence of clinical bleeding. Severe liver disease is regularly associated with abnormalities in hemostasis related in part to prothrombin deficiency, increased capillary fragility, diminution in platelets and sometimes vitamin C deficiency. The complexity of the problem of hemostasis has been emphasized in recent years.[219, 224] The evaluation of a given patient with abnormal bleeding may require extensive laboratory tests. Probably the most useful single laboratory technic is the silicone-clotting determination, which tests the coagulation of whole blood. Unfortunately, this procedure cannot be performed in a routine manner. Normal clotting time in glass tubes is not sufficient by itself to exclude the possibility of abnormal bleeding. Unless reliable laboratory tests for blood coagulation are available, erroneous determinations may give clearance for liver biopsy when the procedure is actually contraindicated. Thus, we have refused requests for needle biopsy despite apparently normal laboratory findings when the patient exhibited purpura or unexplained bleeding. Patients should be questioned routinely for easy bruisability and excessive bleeding from the nose, rectum or vagina. The skin should be examined for petechiae, purpura and ecchymoses, especially at the site of needle injections. Urine and stool specimens should be tested for occult blood. We have abandoned the performance of needle biopsy when bleeding from the routine nick of the skin before the actual introduction of the biopsy needle was unduly prolonged.

In rare cases the risk of needle biopsy may be warranted in certain patients who do not satisfy these criteria. A prothrombin time of 50 per cent may not differ enough physiologically from one of 35 per cent to warrant absolute discriminatory significance. We have performed needle biopsy in patients with prothrombin times of less than 50 per cent after careful evaluation of other coagulation factors. This should not be done,

however, without advice from specialists in blood coagulation. Differing from many workers, Whitesell and Snell[125] believe that in certain purpuric patients liver biopsy is indicated when necessary to distinguish between idopathic thrombocytopenic purpura, for the treatment of which splenectomy may be required, and thrombocytopenia secondary to liver disease, in which splenectomy may be contraindicated. They performed liver biopsies without mishap on 4 patients despite thrombocyte counts reduced to 43,000, 62,000, 67,000 and 75,000, and prothrombin times prolonged to 21 to 25 seconds (compared with normal values of 19 to 20 seconds).

Finally, careful follow-up observation should be made after every needle biopsy. Frequent pulse and blood-pressure readings may give early evidence of bleeding and permit prompt transfusion. Similarly, minimal signs of peritonitis may suggest bile leakage in jaundiced patients, and prompt exploratory laparotomy, with decompression of the biliary tree, may be instituted. Difficulty encountered during the procedure of needle biopsy should alert the physician to the possibility of complication.

Conclusions

A review of 20,016 needle biopsies of the liver indicates clearly that at present this is the most useful adjunct available for the diagnosis of clinical liver disease. In the hands of unqualified persons, misled by its apparent simplicity, the procedure is hazardous, but, when performed by experienced personnel, it is remarkably safe, having a true mortality of less than 1:1000. The proper use of needle biopsy can save many lives by permitting early diagnosis and prompt institution of correct medical or surgical therapy.

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MEDICAL INTELLIGENCE

ISONIAZID IN TUBERCULOUS PSYCHOTIC PATIENTS

MICHAEL A. FERRARA, M.D.,*
AND ELOISE B. PETERSON, M.D.†

NORWICH, CONNECTICUT

WHEN isoniazid (iso-nicotinic acid hydrazide) was first introduced in the treatment of tuberculosis, it was noted that, in contrast to other antituberculosis drugs, it was of low toxicity. Such toxic manifestations as were observed in the early days of its use (involuntary twitching, hyperreflexia, irritability, transient loss of memory, constipation, vertigo, insomnia and difficulty in starting the urinary stream) were transitory and mild, even with the continued use of the drug, and little clinical significance was attached to them. However, with more patients receiving the drug and with increases in dosage, it became apparent that isoniazid could have serious toxic effects. Acute pellagra[1] and polyneuritis[2] have been reported. One of us (M.A.F.) has seen 2 patients who became acutely psychotic and returned to normal with the prompt discontinuance of the drug. Hunter[3] reports a case of confusional psychosis due to isoniazid therapy in which organic cerebral impairment of the Korsakow type remained. The larger doses are not necessarily the cause, for reports from Sweden[2] show that psychotic episodes occurred in patients receiving 4.3 mg. of isoniazid daily per kilogram of body weight.

When it became apparent that isoniazid produced toxic manifestations affecting mainly the central nervous system, some physicians[4] even advocated withholding the drug in patients with organic disease of the central nervous system or with abnormal mental or emotional signs or history. It was decided, therefore, to try to determine the effect of isoniazid on tuberculous patients who were also psychotic. It was not possible, as a control, to administer the isoniazid to a similar group of mentally ill patients who were not tuberculous.

Accordingly, 39 mentally ill, tuberculous patients at the Norwich State Hospital were given isoniazid alone as treatment for their tuberculosis of the lungs for six months, from October, 1952, to April, 1953. The daily regimen consisted of 8 mg. of isoniazid per kilogram of body weight given in equally divided doses, twelve hours apart.‡

Laboratory studies, made before drug therapy and every two months during the study, included the following: complete hemogram, determination of blood urea nitrogen, urinalysis and single posteroanterior roentgenograms of the chest. Sputums were examined once a month for acid-fast bacilli by smear, or culture, of a concentrate of a seventy-two-hour pooled specimen or by culture of gastric specimens. The patients were weighed once weekly.

Of the 39 patients, 25 were men, and 14 were women; 2 were Negroes, and 37 whites. The ages ranged from twenty-nine to ninety-three (Table 1).

The types of psychoses dealt with and the number of patients are shown in Table 2. The duration of mental illness before the start of isoniazid therapy ranged from six months to fifty years, the average being fourteen years.

The tuberculosis was minimal in extent in 8, moderately advanced in 17 and far-advanced in 14

TABLE 1. *Age Distribution.*

AGE	NO. OF PATIENTS
yr.	
20-29	2
30-39	5
40-49	6
50-59	10
60-69	11
70-79	3
80-89	1
90-99	1

TABLE 2. *Types of Psychoses Encountered.*

TYPE OF PSYCHOSIS	NO. OF PATIENTS
Schizophrenic reaction:	
Paranoid type	9
Simple type	2
Hebephrenic type	5
Undifferentiated type	5
Catatonic type	2
Paranoid reaction:	
Paranoia	1
Paranoid state	2
Manic-depressive reaction:	
Depressed type	2
Other	1
Involutional psychotic reaction	1
Mental deficiency, idiopathic, severe	1
Chronic brain syndrome associated with convulsive disorder, with psychotic reaction	1
Sociopathic personality, dysocial reaction	1
Organic brain disease, with various etiologic factors	6
Total	39

*Clinical instructor in medicine, Yale University School of Medicine; assistant superintendent, Uncas-on-Thames.

†Senior physician psychiatrist, Norwich State Hospital.

‡At the start of the study at Norwich State Hospital, the average dosage used in tuberculosis work was 4 mg. per kilogram of body weight. However, in a paper presented by McDermott and his associates at the Connecticut Clinical Congress in New Haven in September, 1952, the results of 5 to 10 mg. in 25 cases of miliary and meningeal tuberculosis were stated to have been so good that the 8-mg. amount was adopted as the standard dose. Since, at the time of the study, there was no definite correlation between high dosage and toxic reactions, it was decided to use the 8-mg.-per-kilogram regimen in view of McDermott's excellent results.

patients. The tuberculosis was diagnosed from three months to twenty-seven years before the start of drug therapy, the average being eight years. All types of tuberculosis were seen: exudative, nodular, fibrotic, calcific, caseous, cavitary and mixed. In all but 2 cases the sputum was positive for acid-fast bacilli at the start of the study, and these 2 patients had in the past produced acid-fast bacilli. Six patients had had streptomycin alone or in combination with para-amino-salicylic acid from three months to one year before the institution of isoniazid therapy.

Somatic therapy for the mental illness was used when indicated during the course of drug therapy.

Discussion

The sputum of 14 patients converted from positive to negative and was still negative three months after cessation of drug treatment. Five of these 14 had cavitary disease, and none of the 14 showed any significant change on x-ray examination.

Of the 39 patients, x-ray study demonstrated no significant change in 32, slight improvement in 3, moderate improvement in 1 and marked improvement in 2. One patient had slight increase in disease. Of the 6 patients with some x-ray improvement, the sputum remained positive in 5 and converted to negative on smear of concentrate in the other.

Except in 1 patient, no serious toxic manifestations were observed that could be attributed to the use of isoniazid.

So far as the lesser side effects of isoniazid are concerned, the patient with the diagnosis of involutional psychotic reaction showed definite euphoric changes. He became less depressed and less agitated a short time after taking isoniazid. Final evaluation was not possible because a prefrontal lobotomy was performed four months after the start of isoniazid therapy.

The greater portion of patients experienced a sense of well-being, which became apparent soon after the start of the drug therapy but lasted only a few weeks. With few exceptions, the patients showed an increase in appetite and gained from 1 to 1½ pounds a week throughout the study. Those not showing this response had been mentally ill for many years and were very regressed.

One patient, a fifty-three-year-old man, had had simple schizophrenia since 1936. He had been practically normal for at least ten years before the use of isoniazid, the only deviation from normal being a diminished affectivity. Two and a half months after the start of drug therapy, he had delusions and hallucinations, neither of which had ever been a part of his mental behavior in the past. This behavior persisted for the last three and a half months of drug treatment. When the drug was discontinued, his active psychotic symptoms were somewhat attenuated, but he continued to react to auditory hallucinations and was still somewhat delusional two and a half months after cessation of therapy.

Because of this, and because of the previous reports and experience as mentioned above, we do not believe that isoniazid is an innocuous drug. It is a potent and useful antituberculous agent, but toxic manifestations involving the central nervous system can occur and should be watched for. When they are present prompt discontinuance of the drug should be seriously considered.

Summary

Thirty-nine tuberculous psychotic patients were given a daily dose of 8 mg. of isoniazid per kilogram of body weight for six months. The sputum of 14 converted to negative. X-ray study showed some x-ray improvement in 6, some worsening in 1 and no change in 32 cases.

One patient, who had been practically normal mentally for ten years before isoniazid therapy, became delusional and hallucinated for the last three and a half months of drug treatment. He did not return to his previous mental status when the drug was discontinued.

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Smog and Anti-Smog—Iced Lollies—Christmas in the Wards

John Lister, M.D.

London, England

As the first anniversary of the disastrous fog of last December appears, the smog consciousness of the nation seems to be reaching a climax. Even through the autumnal "season of mists and mellow fruitfulness," the patients with chronic bronchitis have been thronging their doctors' offices, acutely anxious lest pneumonia supervene, and now, almost daily, there are columns and news items in the national press on the subject of Smog and Anti-Smog. A boom in the sale of surgical gauze and chiffon scarves resulted from the advice of the local Medical Committee of the County of London that the public should protect itself from fog by wearing a simple mask. The committee suggested that one could make an adequate mask, costing only a few pence, by folding strips of gauze into several layers, but the Minister of Health, Mr. Macleod, was quick to denounce the value of such a simple and cheap remedy. Asked in the House about prospective re-

search into the use of suitable respirators to combat thick fog, he said that although gauze masks would impede some of the solid particles, they would be of little value in absorbing toxic gases present in fog, such as sulfur dioxide. He also pointed out that respirators giving protection from gases had been known for many years, but the persons most affected by these gases were sufferers from chronic pulmonary or cardiac disease and special research was being carried out among the outpatients of a large hospital to determine what respirators could be safely worn by such persons for long periods. Despite the Minister's rejection of the simple mask many London drugstores were sold out of surgeons' gauze masks when the first heavy fog hit the City. A woman even bought one for her dog!

At the Royal Sanitary Institute, London, an exhibition demonstrates, with the help of working models, the formation of fog and its effect on health and buildings. Dr. E. T. Wilkins, research scientist to the Institute and officer-in-charge of the Department of Scientific and Industrial Research, has stated that final figures indicate that a total of 12,000 deaths could be attributed to last year's fog. In an illustrated lecture he showed charts of smog density during the foggy period and claimed that domestic fires are responsible for 60 per cent of smoke in winter. He pressed for more smokeless fuels, smokeless zones on the downwind side of polluted areas and perfected methods of banking up fires at night.

In leading articles the *Lancet* and *British Medical Journal* both stress the simple fact that Londoners manufacture their own fogs with the help of the weather and point out that they can overcome the fog menace only by producing less smoke. This has long been the contention of the National Smoke Abatement Society, and the enforcement of smokeless zones is long overdue. They were first suggested in this country by a Manchester barrister, Mr. Charles Gandy, in 1935, when he was chairman of the Smoke Abatement Society. By 1938 Manchester had planned a smokeless city center, but the war held up the scheme, which was not put into effect until 1952. The experiment has met with great success, and many other towns have obtained authority to impose restrictions on smoke. In particular, the City of London recently announced its intention of seeking statutory powers to establish a smokeless zone within the City. In such a zone the emission of smoke from any building is prohibited, but the ban does not cover railway locomotives. The creation of these zones is not without difficulties, since many interests are concerned. To overcome resistance it is necessary to show the public not only that smoke is a harmful nuisance but also that it is indicative of waste. Owners and tenants of premises within proposed zones must be consulted, and expert advice made available to them on any necessary conversion of fuel-burning appliances.

Whatever the opposition to the extension of smokeless zones, it is incumbent on the medical profession to press for them wherever local industrial and local weather conditions are likely to conspire to cause smog. It certainly looks as though the days of the English coal fire were numbered.

* * *

When I visited the United States I was greatly taken with the Howard Johnson hoarding advertising the sale of ice cream in 28 flavors. I cannot recall whether these flavors included anything resembling the iced lolly we know over here. I rather doubt it, for not only have these water ices mounted on sticks no food value but also certain of their species have recently been shown to contain significant amounts of copper, zinc and lead.

When asked in Parliament to set a national standard for iced lollies, Dr. Charles Hill, Parliamentary Secretary to the Ministry of Food, had first to define the lolly. He explained that it is "water with a fruit flavour that has been frozen" and not, as one member surmised, "a lollipop with the pop taken out."

Interest in the lolly was first aroused by the report of Semple in 1953 that these fashionable confections of varied and often hideous hue may contain up to 11 parts per million of lead. Copper, tin and zinc may be present in amounts up to 11, 7 and 5 parts per million, but these concetrations are not high enough to be harmful. On the other hand, the concentration of lead is undesirably high and could conceivably cause lead intoxication if sufficient lollies were consumed. It has been shown that the chief source of the lead is in the molds in which the water and colored syrups are frozen. Consequently, it is clear that one may prevent contamination by ensuring that only suitable nonmetallic containers are used in the preparation of the lollies, and it seems reasonable to make it illegal to sell lollies containing lead in a higher concentration than that found in the local drinking water.

Nevertheless, reviewing the situation in the light of the evidence, a cynical doctor remarked that it might do people less harm if they "left the lollipop and swallowed the stick."

* * *

Weeks before Christmas there were signs of preparation in the wards. Decorations were made by patients; lamp shades of crepe paper were cut out, and Christmas tree trinkets collected. On Christmas Eve the decorations go up, the trees are trundled in, and there is fierce competition among the nursing staff to see which ward will be acclaimed the best decorated. Indeed, when work is completed each ward looks more like a children's mystery corner in a Department Store than part of a hospital. Before the lights are finally dimmed, the carol party of nurses and doctors tours the hospital and

then all is quiet until Christmas morning, when Santa Claus (usually one of the interns) visits each ward fully clad in scarlet robes and distributes the patients' gifts. During the morning it is customary for all the doctors who normally work in the ward to make "Grand Rounds" with their wives and children, and there is usually a gift on the tree for every young visitor.

At mid-day comes the climax, when the turkey is ceremonially carved by a senior surgeon or physician who wears a chef's apron and hat for the occasion. After the Christmas dinner the postprandial stupor is profound, but the party is not yet over, for, later in the day, the interns entertain the patients in song and jest, which is usually at the expense of the more senior members of the hospital staff. Although next day the diabetic patients may show sugar, the gastric patients complain of discomfort and the temperature charts reveal an undulant fever, most patients will agree that they have never had a better Christmas than the one they spent in the hospital.

CONSULTANT'S OPINION

THE following letter has been submitted to the *Journal* by Dr. Robin Smith, of Neenah, Wisconsin.

It was sent nearly a hundred and one years ago, to the day, to his great-grandfather, Dr. N. S. Robinson, then a practitioner in Dover-Foxcroft, Maine.

The consultant in the case of Mrs. Hudson was almost certainly Dr. Walter Channing, who was admitted to the Massachusetts Medical Society in 1814, retired in 1854 and died in 1876 at the age of ninety.

Dr. Channing, one-time treasurer of the Society, was a founder of the *New England Journal of Medicine and Surgery* in 1812 and one of its first editors.

Boston, December 26, 1852

Dr. Robinson — Dear Sir —

I have examined the case of Mrs. Hudson. She has for some years suffered from pain in the right side, increased by lying on that side, and by pressure. I cannot detect any enlargement of the liver, and the pain is above its ordinary seat. There has been no functional disturbance of the organ, no deficiency of bile . . . by yellowness of the skin, or of the conjunctiva. Under these circumstances may we not regard it as a voracious modification of neuralgia, rather than dependent on organic union of any organ. In view of this I have thought that a treatment which would meet both in directions, whether of neuralgia or chronic hepatic trouble may be tried. I would recommend sponging the side once or twice a day with the nitro-muristic bath, say with water made as acid as common vinegar. I would advise the wearing of flannel to prevent injuring the skin by the acid. This may be continued some time, . . . its advantage may be derived from its counter-irritant power, and from its specific agencies.

The uterus was carefully examined by touch and by speculum. There is normal *tenderness*, either *in it*, or in the region of the ovaries. But there is ulceration above, and in the os, and a dense, inspissated leukorrheal discharge, around and exuding from it. For this the nitrate of silver in solution or substance may be very carefully applied. I applied the former fully, and its effect may be noticed by her *sensations*, and by examination. The discharge should be carefully washed off by sponge and water, or a brush before the nitrate is used. The back, hips and lower part of the abdomen may be carefully rubbed once a day with a strong brine of salt and water.

For the trouble in the *side*, I would recommend a slightly alternative and tonic pill as follows:

Rx: Quinine sulphate: drams i
Extract comii : grains x
ext. Tanaxii : grains ii
M ft. pic. no. XX
one three or four times a day.

If heart be troubled by the pill, give it only twice or thrice a day, and half instead of a whole pill.

Exercise, moderate, or not reaching fatigue.

Diet. Morning and evening meals. Shells, or cocoa, fresh butter; an egg or two.

Dinner. Some meat if well digested. Avoid tea, coffee, cake, pastry, and all indigestible food.

I have thus gone into some detail. (The nitrate I meant to say may be applied twice a week.) I trust you will pardon me for minuteness in regard to remedies, and the mode of exhibition above suggested. I knew of no better way of stating exactly what a case submitted for consultation may seem to require. Still the adoption of some suggestions must always depend on the views taken of them by him to whom they are made. I submit them entirely to your judgment.

Accept my best thanks for the confidence reposed in me by your recommendation of Mrs. H. to my examination, and believe me when I add that I shall always be happy to hear from you, and of your success.

I remain yours very truly,

DR. CHANNING

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 39521

PRESENTATION OF CASE

A seventy-six-year-old retired stagehand was admitted to the hospital because of increasing dyspnea and paroxysms of coughing.

The patient had given up touring in road shows at the age of forty-six years because of an annoying morning cough, which was productive of "chunks" of yellow sputum. At this time allegedly moderate exertional dyspnea appeared, apparently persisting thereafter. Despite these symptoms he worked intermittently without much difficulty until about seven months before admission. There had never been any cyanosis, hemoptysis or chest pain. For a number of years he had preferred to sleep on two pillows. During the six months preceding admission he had noted some increase in severity of dyspnea but had done fairly well except for anorexia until about four weeks before entry. At that time there was the onset of what he interpreted as a "chest cold," characterized by markedly increased cough, dyspnea and orthopnea. Approximately three weeks before admission he began to experience bouts of paroxysmal nocturnal dyspnea with "wheezing." A week later he consulted his physician, who told him that he had a "tired heart" and placed him on digitoxin, Mercuhydrin, ammonium chloride, penicillin and streptomycin. About four or five days after the initiation of this therapy pedal edema developed, and the cough became more frequent and productive of "bubbly," whitish-yellow sputum that was not blood-tinged. By this time he was severely orthopneic. Five days before and on the night preceding admission he had suffered bouts of severe paroxysmal nocturnal dyspnea.

There was no history of chills, fever, night sweats, weight loss or chest pain either in the past or during the more recent phase of his illness. He had had occasional brief episodes of precordial "oppression" seemingly brought on by coughing or emotional upsets. The past history was otherwise noncontributory except for a two weeks' illness in 1918, when he was forty-one years old, diagnosed as pneumonia. The patient's wife had died three years previously of pulmonary disease manifested clinically by increasing cough and dyspnea; roentgenograms of the chest had revealed a "dense, honey-combed" appearance of the entire left lung, with numerous shadows interpreted as cavities, but attempts to establish the etiology were unsuccessful.

Physical examination revealed a ruddy-faced, markedly dyspneic and orthopneic, slightly obese man who exhibited slight cyanosis, which became more prominent during paroxysms of coughing. He was tachypneic, with a prolonged expiratory phase. The neck veins were distended to a level 4.0 cm. above the clavicles when the patient was raised to 60°. The chest showed a slight increase in the anteroposterior diameter. Fine and medium rales and wheezes were heard over all lung fields but particularly below the scapulas. The heart was believed to be moderately enlarged. There was a regular, rapid rhythm without gallop, and a soft, blowing systolic murmur was heard over the entire precordium. The aortic and pulmonic second sounds were equal. The liver edge was palpable 4.0 cm. below the right costal margin. No other organs or masses were palpable. Pitting edema was present up to the high calf region and was + to ++ over the sacrum. There was no clubbing of the fingers.

The temperature was 99°F., the pulse 120, and the respirations 28. The blood pressure was 110 systolic, 60 diastolic.

Urinalysis revealed a specific gravity of 1.020 and a + test for albumin; occasional hyaline and granular casts were seen in the sediment. Examination of the blood disclosed a hemoglobin of 15.6 gm. per 100 cc. and a white-cell count of 12,000, with 90 per cent neutrophils, 7 per cent lymphocytes and 3 per cent monocytes. The serum chloride was 101 milliequiv., the sodium 134 milliequiv., the potassium 4.5 milliequiv., and the carbon dioxide 32 milliequiv. per liter, and the nonprotein nitrogen 78 mg. per 100 cc., later falling to normal levels. An electrocardiogram taken shortly after admission (and after digitalization) revealed a PR interval of 0.26 second and a QRS interval of 0.09 second. Changes of a slight left-axis deviation were manifested by the standard leads. RSR′ waves were present in Lead V_2. The ST segments sagged in Leads 1, 2, aVL, V_3, V_4, V_5 and V_6. The T waves were low and upright in Leads 1, 2, aVL, aVF, V_2, V_3, V_4, V_5 and V_6. The rate was regular at 104 per minute. A roentgenogram of the chest showed extensive areas of consolidation throughout both lungs, particularly on the left side (Fig. 1).

Upon admission the patient was placed in an oxygen tent, digitalized, sedated and given a mercurial diuretic. Within the ensuing twenty-four hours

there was very slight symptomatic improvement in the face of increasingly apparent physical signs of consolidation or fluid at the left base.

The subsequent course was one of progression of symptoms interspersed with brief periods of improvement. A variety of antibiotics proved ineffective; the white-cell count remained high, reaching 24,000 terminally. Blood cultures were negative, and cytologic studies of the sputum were negative for tumor cells. The course was also complicated by loss of pulsations in the right posterior tibial and dorsalis pedis arteries, with ischemia of the foot although this subsequently cleared. Additional roentgenograms of the chest failed to demonstrate any significant change. Terminally, dyspnea was more severe, and the cough was productive of copious amounts of tenacious, yellowish, occasionally blood-tinged sputum. Rales were more numerous. The patient died on the twentieth hospital day, three hours after a therapeutic bronchoscopy, which revealed no abnormalities except edema and congestion of the mucous membranes and copious secretions.

FIGURE 1. *Roentgenogram of the Chest.*

DIFFERENTIAL DIAGNOSIS

DR. JOHN W. CASS, JR.*: This seventy-six-year-old man had symptoms of cardiac or pulmonary disease of twenty years' duration that during most of this time did not prevent him from doing some sort of work but not his original job. During the final stage of the disease, the last few weeks, he was in myocardial failure that was not responding to the ordinary procedures. It does not seem possible to make a diagnosis of primary heart disease although the duration of the condition and the symptoms could have been on a cardiac basis. Nothing in the history suggests any primary heart disease—no history of rheumatism or any other condition that may have resulted in myocardial failure. The physical examination provided no definite evidence of primary heart disease. The heart was stated to be moderately enlarged. There was a systolic murmur over the entire precordium. The aortic second sound was equal to the pulmonic, which is a little surprising (in this age group one would expect the aortic second sound to be louder than the pulmonic), and I think that the pulmonic second sound was probably actually accentuated. There were minor electrocardiographic changes—a prolonged PR interval and slight left-axis deviation—but not enough for me to make a diagnosis of primary heart disease. Nothing in the laboratory work or course of treatment indicated specific heart disease. Although some type of heart disease must have been present, I am sure it must have been secondary.

There was no evidence that this patient had chronic renal disease. There was an elevated nonprotein nitrogen and carbon dioxide combining power, but in a man of seventy-six who was in cardiac failure and in whom the nonprotein nitrogen is known to have returned to a normal level, that is not sufficient evidence of renal disease.

I believe the heart disease must have been secondary to pulmonary disease. There was a history of pulmonary disease although it was not specific for any particular type. He had progressive cough, dyspnea, sputum and a terminal condition that was apparently complete respiratory failure; it sounds as though he drowned in his own secretions. There was a desperate effort to help him by bronchoscopy, which the physicians would not have done if they had been dealing with definite pulmonary edema on a cardiac basis. The problem of diagnosis boils down to what clues can be obtained from the x-ray films, possibly from sputum studies and probably from biopsy of the lung. I think it is wise to look at the x-ray films now.

DR. STANLEY M. WYMAN: Three examinations were done—the first two, one day apart and the last, ten days after the initial examination. There is an extensive process involving the entire left lung with mottled hazy densities that are not homogeneous (Fig. 1). There is a similar, less pronounced process in the right lung. The heart shadow can be seen only imperfectly on the first two films but fairly well on the third; it is not obviously enlarged; it seems to be within normal limits. The pulmonary vessels cannot be identified individually. There is only a small amount of fluid in the right pleural space; there may be some in the left. The process in the lungs seems

*Assistant physician, Massachusetts General Hospital.

to be uniform, but the amount of density may be accentuated in the base of the left lung posteriorly.

DR. CASS: Was he fluoroscoped?

DR. WYMAN: No; he probably was too sick to be fluoroscoped.

DR. CASS: There is certainly no cavitation. Both leaves of the diaphragm are quite normal.

DR. WYMAN: Both leaves seem to be in a normal position. There is no obvious cavitation; there are interspersed rarefactions, but I think they are areas of preserved lung. The last two films show a suggestion of some clearing of the process in the right lung; the left lung may be a little less dense than it was originally. This suggests that there is some clearing of an acute process superimposed on something else or of an acute accompanying process, perhaps.

DR. CASS: The x-ray films are very helpful; they immediately rule out certain pulmonary conditions. I am sure from the x-ray films that this man's primary disease was in the lung and that it is unlikely that he had any specific type of heart disease. There are only two facts in the history, other than the long course, that are of help in determining the etiology of the disease. The first is that in 1918 the patient had some sort of pneumonia, which may have been influenza; if so that may have been the start of a chain of repeated infections resulting in a great deal of lung destruction over the years. There was, however, no history of repeated pneumonia; also, the x-ray films do not seem to show any great amount of fibrosis or emphysema. The second helpful fact is that his wife died with a pulmonary illness characterized by cavity formation, which I assume was tuberculosis, so that he had a questionable exposure to tuberculosis. The x-ray films do not definitely suggest tuberculosis, but I cannot rule it out. Tuberculosis in the aged can be entirely a fibrotic disease, and it can be difficult to obtain positive sputum. Those patients die eventually not with the picture of pulmonary sepsis but with pulmonary insufficiency and cardiac failure. On the basis of the history and with the x-ray findings, I cannot make a definite decision about the etiology.

The sputum is the next basis upon which it is possible to make a diagnosis. The description of the sputum is not too helpful. It was an abundant, drowning type of sputum toward the end so it should have been fairly easy with the proper studies to decide whether any type of infection, including tuberculosis, was present. It seems fairly reasonable, therefore, to assume that this was not tuberculosis. The sputum on a single examination contained no tumor cells.

A specific diagnosis of the pulmonary disease may be only academic after the conditions, like tuberculosis, that can be treated specifically are ruled out. To make a definite diagnosis in this case would probably require a biopsy of the lung. Apparently, the diagnosis was brought to a point where treatment was clear and that was all that was necessary. The disease did not respond to antibiotics as it should have done at least temporarily if it had been one of the ordinary infections, excluding tuberculosis. There was no response to cardiac therapy. The pulmonary disease was so far advanced that he had myocardial failure only as a terminal event, and that type of heart disease quite characteristically does not respond to therapy except briefly and temporarily.

By a process of elimination I have chosen a rare, diffuse pulmonary disease such as pulmonary adenomatosis and believe that he died with pulmonary edema in myocardial failure.

DR. RONALD C. SNIFFEN: Apparently, the service had a great deal of trouble treating this man.

A PHYSICIAN: Our reasoning was along the line of Dr. Cass'. The patient's failure to respond to the various measures led us to believe that he had some sort of diffuse pulmonary disease such as adenomatosis.

DR. ALLEN G. BRAILEY: What did Dr. Cass think about embolization?

DR. CASS: I should have mentioned that. I thought it was incidental in a man of seventy-six in a terminal stage.

A PHYSICIAN: Could this have been due to beryllium?

DR. SNIFFEN: Not so far as we know.

DR. CASS: I do not think the x-ray findings or clinical picture are like those seen with beryllium disease.

DR. WYMAN: I had thought of adenomatosis or some bronchogenic tumor as the more likely possibility. I think that Dr. Cass is correct in believing that the patient must have had some superimposed pulmonary edema. I wonder if that copious watery sputum is not a lead in the direction of adenomatosis.

CLINICAL DIAGNOSES

Staphylococcal pneumonitis.
?Alveolar-cell carcinoma.
Chronic pneumonitis.
Arteriosclerotic heart disease.

DR. JOHN W. CASS' DIAGNOSES

Diffuse pulmonary disease, ?adenomatosis.
Pulmonary edema.
Cor pulmonale, with failure.

ANATOMICAL DIAGNOSES

Chronic pneumonitis, type undetermined.
Cor pulmonale.
Hemorrhagic necrosis of adrenal glands.
Thrombosis of popliteal artery, right, and leg veins.
Adenocarcinoma of prostate.

Pathological Discussion

Dr. Sniffen: At the time of death the patient had several incidental findings. There was thrombosis of the right popliteal artery and deep veins of the calf, with early gangrene of the foot. Also, he had a small adenocarcinoma of the prostate.

The heart was not enlarged, weighing 290 gm. However, the right ventricle measured 7 mm. in thickness — a definite cor pulmonale, particularly in the presence of a dilated ventricle. The left ventricle was approximately normal. The lymph nodes of the mediastinum and the bronchial lymph nodes were large but not otherwise remarkable. The right pleural cavity contained 70 cc. of clear fluid and no adhesions; the left side was completely obliterated by adhesions.

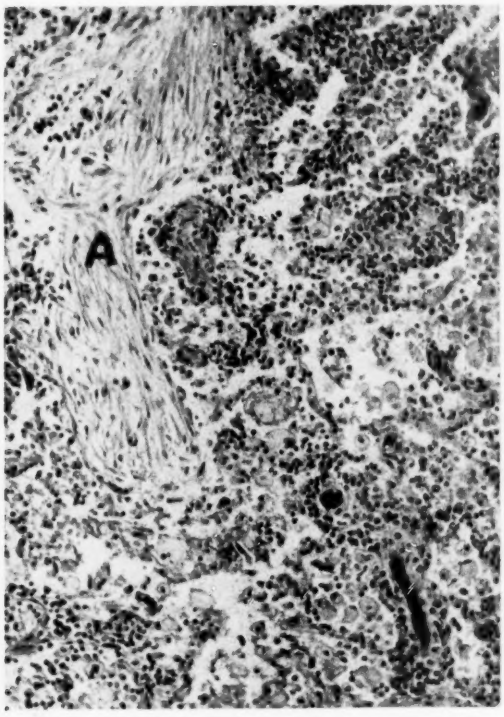

Figure 2. *Photomicrograph of the Lung, Showing Severe Chronic Interstitial Pneumonitis, Lipophages in the Air Spaces and Organization of Exudate in the Alveolar Ducts* (A).

The lungs were quite remarkable. Both of them were consolidated and cut like liver. The left lung was more extensively diseased and almost completely consolidated in a rather odd way, in that there were large, firm nodules, which apparently had become confluent. The lesions were grayish, rather glassy and distinctly mucoid. The left lower lobe was completely consolidated but still gave the impression of nodularity. The bronchi were plugged with tenacious yellow exudate, which welled up into the trachea.

The microscopical findings were unusual. There was a chronic bronchitis, with desquamation of the epithelium and infiltration of the wall by lymphocytes and plasma cells and a few neutrophils and eosinophils. The inflammatory process in the parenchyma was largely interstitial (Fig. 2). The walls of the air spaces were thickened, in some areas greatly so, and infiltrated with the same types of inflammatory cells; alveolar epithelialization was prominent. The alveoli were largely obliterated, and the remaining air spaces contained scattered lymphocytes and plasma cells and foci of macrophages. Occasional buds of granulation tissue had grown into the bronchioles and alveolar ducts. In a few areas the parenchyma had lost its architecture, and all that remained was a reticulum infiltrated with inflammatory cells. In an occasional field the process resembled so-called cholesterol pneumonitis in that the reaction was interstitial and was characterized by many foam cells, containing various lipids, cholesterol and cholesterol esters, within the air spaces.

The etiology of the condition is distinctly nebulous. Reports of this type of pneumonia are not infrequent in the literature.[1] The last one that was brought to my attention included a man in his thirties,[2] who showed the same rapid respiratory incapacitation and x-ray picture as this patient. Antibiotics were ineffective and he was intensively studied for bacterial and viral agents without reward; skin tests were negative. He was given ACTH for a week or so, and the lungs cleared remarkably. Then during another week ACTH was gradually discontinued, and the patient was ambulatory around the ward, when suddenly he became severely cyanotic and dyspneic and died within a couple of days, four weeks after the onset. Fienberg,[3] who has reported several similar cases, has tried to link the disease with cholesterol pneumonitis; he has also reported cases in which there were necrotizing granulomas in the lungs and similar granulomas in the kidney. He suggests that the process may be a manifestation of the Arthus phenomenon in the bronchi and that the changes in the parenchyma are secondary to bronchial obstruction. Oddly enough, the patient under discussion had massive hemorrhagic necrosis of both adrenal glands, with thrombi in the capillaries.

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CASE 39522

Presentation of Case

First admission. A four-month-old boy was admitted to the hospital because of an exacerbation of intermittent diarrhea that had been present since the third week of life.

The pregnancy of the mother and the birth of the child had been uneventful. His birth weight was 7 pounds, 14 ounces, and he was sent home on a formula of evaporated milk, 250 cc., water, 250 cc., and Karo, 60 cc., with feedings every three hours. He did well until two weeks of age, when foul-smelling, watery stools were noticed. The formula was altered; however, the diarrhea continued. When, at the age of one month, he was admitted to another hospital, he was placed on a diet of whole boiled skim milk and banana flakes, and the diarrhea lessened. He was sent home to continue on this diet, together with rice cereal and, later, vegetables. He gained weight, but the diarrhea still persisted with about six loose, foul-smelling stools a day. When a vitamin supplement was started, a rash appeared that disappeared when the supplement was withdrawn. At three months of age, the stools had increased to twelve a day. Two weeks before admission, dark blood was seen in a stool, and on the same day two additional stools were described as consisting of red blood alone. The patient was readmitted to the other hospital to be discharged the next day on the same diet but with Bremil (milk preparation) added. One week before admission here he had a running nose, and two days later became hot, and vomited. A physician made the diagnosis of an abscessed ear, and the patient was again admitted to the other hospital, where he was given penicillin and a sulfonamide. He was treated with clyses and improved somewhat, but the diarrhea and vomiting again grew severe, and he was transferred to this hospital.

The mother suffered from hay fever, and a half sister aged nine years was said to be allergic to costume jewelry.

Physical examination showed an alert, well hydrated boy in no apparent distress. The abdomen was slightly protuberant, and tympanitic. The ear drums were not abnormal. The pharynx was minimally injected. A Grade 1 systolic murmur was heard over the aortic area. The scrotum and thighs were edematous from the clyses.

The temperature was 100°F. by rectum, the pulse 90, and the respirations 20.

Urinalysis was negative. The hemoglobin was 10 gm. per 100 cc., and the white-cell count 12,000, with 35 per cent neutrophils, 56 per cent lymphocytes, 5 per cent monocytes, 2 per cent eosinophils and 1 per cent basophils. The white-cell count fell to 8000 on the second hospital day. The serum pH was 7.52, and the carbon dioxide 24 milliequiv., the sodium 144 milliequiv., the potassium 3.1 milliequiv., and the chloride 115 milliequiv. per liter; the total protein was 4.4 gm., the calcium 8.4 mg., and the phosphorus 2.8 mg. per 100 cc. Five days after admission, the total protein was 5.2 gm., the albumin 3.6 gm., and the globulin 1.6 gm. per 100 cc. At this time the alkaline phosphatase was 16.3 units per 100 cc., and cephalin flocculation was + in forty-eight hours. A blood Hinton test was negative. Stools were repeatedly guaiac negative, and were without pus cells. Cultures of the stools were negative for pathogens, as were cultures of the nose, throat and urine. Hollister-Stier skin tests were negative with wheat, beef and egg white and equivocal with cow's milk. Intradermal tests were perhaps slightly positive with egg white and wheat and slightly more positive with cow's milk. An initial roentgenogram of the chest showed an area of increased density in the left lower lobe suggesting pneumonitis, but a later film was clear. A plain film of the abdomen revealed a considerable amount of gas throughout the bowel, but did not suggest obstruction. On an intravenous pyelogram there was prompt excretion of dye on both sides, although intestinal gas obscured detail.

The patient was started on an oral potassium solution with 10 per cent dextrose and water. The diarrhea decreased abruptly, and finally disappeared. A nutramigen formula was started, and was gradually increased to full strength. Boiled cow's milk was gradually substituted, until the patient was discharged on the thirteenth hospital day on whole boiled cow's milk with supplementary feedings of cereal and vegetables. He was having only one or two bowel movements a day.

Second admission (eight days later). He had been well until five days before admission, when he was seen to strain, at which time he passed a stool that was slightly firmer than normal but otherwise not remarkable. Later that day he passed bright-red blood admixed with stool.

Since that time he had had stools twice each day with a large amount of "dark-brownish" blood and black clots admixed with the stool. The mother noticed that the patient had gradually become pale, weak and unusually restless; for the past two days he had appeared pale, sweaty and weak immediately after each bowel movement. On the morning of the day of admission he was seen by the family physician, who found the blood hemoglobin to be 6.4 gm. per 100 cc. Hospitalization was advised.

Physical examination showed a pale, fretful child. There was slight coryza and slight injection of the fauces. On rectal examination the feces were grossly bloody. The examination was otherwise negative.

The temperature was 100.4°F. by rectum, the pulse rate 140, and the respirations 30. The blood pressure was not determined.

The urine had a specific gravity of 1.005 and was normal. The hemoglobin was 4.6 gm. per 100 cc.,

and the white-cell count 26,950, with 37 per cent neutrophils, 60 per cent lymphocytes and 3 per cent monocytes. Two transfusions of 90 and 80 cc. of blood were given at once, after which the hemoglobin rose to 11 gm. per 100 cc. and remained at that level. The white-cell count fell to 12,700. The patient was continued on the Mulsoy (hypoallergenic milk formula) formula and improved. The stools were consistently guaiac positive for the first three hospital days, but then became guaiac negative. At no time were there more than two stools a day. After the transfusions, the bleeding time was six and a half minutes, the clotting time seven and a half minutes; and the prothrombin time 73 per cent. Proctoscopic examination was negative. A plain film of the abdomen and a barium-enema examination were unremarkable.

On the eighth hospital day an operation was performed.

Differential Diagnosis

Dr. Robert M. Todd*: Diarrhea developed shortly after birth, and this infant continued to pass foul-smelling stools for about three months; at that time blood was first noticed in the stool but for only a few days. Then he had a respiratory infection, which responded to antibiotics, but the diarrhea continued and he became dehydrated and was given clyses. At that stage his abdomen was slightly protuberant and tympanitic. After treatment with potassium and glucose solutions the diarrhea ceased, and a week later he passed blood sufficient to reduce the hemoglobin to 4.6 gm. per 100 cc.

With that story I have to consider first infection in the alimentary tract. The protocol states that the stool cultures were negative for pathogens, which I assume were the dysentery and salmonella groups. Other organisms, particularly *Escherichia coli* of the 0.111 and 0.55 groups, have something to do with gastroenteritis in infancy, but in this case I do not think the natural history of the disease favors this diagnosis. Similarly, ulcerative colitis, if we can consider this an infection, is not suggested by the history. There was no history that mucus had been passed, and certainly no tenderness along the course of the colon, which one finds in that disease. From the history it is obvious that a milk allergy was considered, but there was very little to support it. There was no associated urticaria, eczema or asthma, no stool eosinophilia and little evidence from the intradermal tests, although these would not negate the diagnosis. I cannot explain the severe loss of blood on this diagnosis.

Pancreatic fibrosis, another condition that is relatively common in infancy, certainly has to be considered in an infant who passed foul-smelling stools beginning shortly after birth and continuing for some time. But a gain in weight and a sudden cessation of the diarrhea in pancreatic fibrosis are unusual. Furthermore, the stools were not described as fatty. Another point is that the quick recovery from a respiratory infection is very unusual with pancreatic fibrosis. Once these patients get an infection it is extremely difficult for them to get rid of it. There was no record of estimation of the trypsin, either in the duodenal juice or in the stools, which would have helped to exclude this diagnosis. Severe bleeding is not a feature of pancreatic fibrosis, but one could explain some bleeding by a vitamin K deficiency due to faulty absorption of this fat-soluble vitamin.

The blood dyscrasias have to be considered since they can give rise to severe bleeding from the intestinal tract, but usually with this severe type of bleeding with a blood disease there is some evidence of bleeding in other parts of the body such as purpura or ecchymoses. It is possible because of the chronic diarrhea that vitamin C played some part in the bleeding, but I think that in every case of scurvy there are red cells in the urine and examination of the urine in this case was negative.

Hemangioma of the small intestines has been recorded in childhood at a very early age but I do not think that is likely here. In many of the cases with this severity of bleeding there are other hemangiomas, particularly on the skin. With intestinal hemangiomas some mucus might be passed, but not foul-smelling stools, which were recorded. Intestinal polyps may cause bleeding, but usually of a minor degree. About 80 per cent of them are found in the rectum, but in this child proctoscopic examination was negative. Sometimes they are found in the colon and may be observed by barium-enema examination. Again, there were negative radiologic findings, but that does not exclude a polyp. I should say that it would be very unlikely for a polyp to give rise to such severe bleeding.

Intussusception may arise from a polyp or from some other cause. The characteristic feature is recurrent colicky abdominal pain; in the protocol there is no mention of any sort of pain in association with the patient's condition. Moreover, a tumor is palpable in about 8 out of 10 cases, and there was no record of a palpable mass here.

Finally, I come to what I consider the most likely diagnosis, a congenital anomaly of the intestine. Meckel's diverticulum is probably the commonest cause of painless profuse bleeding in this age group, and I should consider that that would be a very adequate explanation for the bleeding that occurred in this child. Probably, there was also some associated malrotation of the intestines and an intermittent obstruction. It is significant, I think, that on one occasion the abdomen was protuberant and tympanitic. Several cases of congenital intestinal anomalies causing chronic diarrhea of the celiac type in young infants have been reported with an abnor-

*Senior lecturer in child health, Liverpool University, England; clinical and research fellow, Children's Medical Service, Massachusetts General Hospital.

mality of the intestine such as a high cecum bound down to the duodenum by so-called Ladd bands; when the bands are divided the celiac symptoms disappear.

I believe in this particular case that a Meckel diverticulum was present with an associated anomaly of development of the small bowel such as a malrotation that could have been responsible for the intestinal symptoms.

A PHYSICIAN: Would you consider duplication?

DR. TODD: I did not specify it in the intestinal abnormalities because I did not have anything to go on, but I think that should be considered.

DR. BENJAMIN CASTLEMAN: Would there be a long history of diarrhea with Meckel's diverticulum alone?

DR. TODD: Unless it was producing some interference with absorption from the bowel, I do not think Meckel's diverticulum would produce the diarrheal symptoms.

DR. NATHAN TALBOT: I wonder if the potassium insufficiency, which may be characterized by either diarrhea or atony of the gastrointestinal tract, would not be a satisfactory explanation for the chronic phase of the diarrhea. Such potassium-insufficiency diarrhea has been produced experimentally in animals. It stops promptly when the potassium deficit is eliminated.

DR. TODD: I think that might explain the late but not the initial diarrhea.

CLINICAL DIAGNOSIS

Meckel's diverticulum.

DR. ROBERT M. TODD'S DIAGNOSES

Meckel's diverticulum.
Malrotation of intestine.

ANATOMICAL DIAGNOSIS

Peptic ulcer in Meckel's diverticulum.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: The surgeons, who agreed with Dr. Todd that the probable diagnosis was a Meckel diverticulum, operated on the patient, and found 60 cm. from the ileocecal valve a characteristic Meckel diverticulum, which was resected along with a small portion of the ileum. On gross examination the diverticulum contained an ulceration, which microscopically proved to be of the peptic type, with the characteristic fibrinoid necrosis of the base. As was expected the ulcer was in the small-bowel epithelium, and adjacent to it was gastric epithelium, the source of the hydrochloric acid necessary for the production of the ulcer. It is the peptic nature of the ulcer in the Meckel diverticulum that is strong evidence for the acid theory of the pathogenesis of peptic ulcer.* As far as I know there were no other anomalies; at least the surgeon, who looked carefully, found no other anomalies in the abdomen. The explanation of the diarrhea suggested by Dr. Talbot, potassium insufficiency, is a good possibility. This is borne out by the fact that the diarrhea stopped after potassium was given during the first admission. The diarrhea apparently masked the bleeding at that time.

*Lindau, A., and Wulff, H. Peptic genesis of gastric and duodenal ulcer: especially in light of ulcers in Meckel's diverticulum and postoperative ulcers in jejunum. *Surg., Gynec. & Obst.* 53:621-634, 1931.

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PRESIDENT WESSELL

The institutions under which the three medical schools in Boston are operated each inaugurated new administrative leaders in the recent past. Well served by Dr. Leonard Carmichael during the fifteen years that preceded his call to the Smithsonian Institution, Tufts College, the latest to make a change, brings to its presidential chair Nils Yngve Wessell. On December 9 Dr. Wessell was installed as the seventh president of Tufts College since it established its medical school in 1893. He came to Tufts in 1939 as dean of the College of Liberal Arts and assistant professor of psychology; he became associate professor in 1945 and full professor of psychology in 1947. After 1951 he served the College as vice-president, and was acting president for a few months directly before his present appointment.

The son of a Congregational Minister, President Wessell was born in 1914. He graduated from Lafayette College in 1934 and received the M.S. degree from Brown University in 1935, the Ph.D. degree from the University of Rochester in 1938 and the honorary degree of Doctor of Science from his alma mater in 1951. Trained in psychology, President Wessell has demonstrated a special interest in the clinical activities of his field, having served as resident psychologist at the Bradley Home and Hospital (for neurologic and behavior disorders of children) and as director of the Mobile Child Guidance Clinic at the University of Michigan. Since 1947 he has been consultant in psychology at the Tewksbury State Hospital, the Massachusetts Hospital School and the Lesley-Ellis School. In 1948–1949 he was chairman of the advisory committee of the Veterans Administration Guidance Center at Harvard University. Clinical interest in fields so closely related to the practice of medicine vouchsafe a sympathetic concern with the problems of medical education.

Among the organizations in which Dr. Wessell holds fellowship are the American Psychological Association, Massachusetts Society for Clinical Psychologists, American Association for the Advancement of Science and Sigma Xi and Phi Beta Kappa fraternities. He is also a member of the American Association of Academic Deans, College Entrance Examination Board, Eastern Association of College Deans, American College Personnel Association, Massachusetts Schoolmasters Club, New England Association of Colleges and Secondary Schools and New England Conference on Graduate Education.

In community life President Wessell has served over a widely diversified field, including the following activities: chairman of School and College Group of Greater Boston United War Fund in 1945; chairman of the Institutions Division of the same organization in 1946; member of Speakers Bureau of American Red Cross since 1946; chairman of Massachusetts Colleges Crusade for Freedom in 1951; member of Board of Managers of Middlesex County National Bank; member of Board of Governors of Swedish-American Council of Boston; member of Educational Commission of the National Conference

of Christians and Jews; and trustee of the New England Colleges Fund.

In 1938 President Wessell was married to Marian Sigler, of Kansas City, Missouri. They have a daughter and a son, aged twelve and ten, and have lived on the Tufts campus in Medford since coming to Massachusetts. The *Journal* extends to President Wessell and his College its best wishes for a long and prospering administration of the affairs of one of the leading educational institutions of this region, and particularly of its medical branch and interest.

RETURN OF RIP VAN WINKLE

THE *Journal* of March 19, 1953 contained an article on "Group Practice with Branch Centers in a Rural County" by Dr. Caldwell B. Esselstyn. The paper, which had been presented at a meeting of the Medical Care Section of the American Public Health Association at Cleveland in October, 1952, described the organization and operation of the Rip Van Winkle Clinic, established six and a half years before in Columbia County, New York.

Numerous members of the Columbia County Medical Society took exception to Dr. Esselstyn's paper. In concerted action they despatched a long letter to the editor, signed by no less than twenty-five of their number. This communication, which was published on July 30, indicated that the doctors of Columbia County, and others, disagreed with some of the statements made in Dr. Esselstyn's paper.

Among other things the letter claimed, in regard to the status of the Rip Van Winkle Clinic as a cancer-detection center, that "either through an oversight or through falsification of the application for approval, the American College of Surgeons carried this center on its 'Approval Lists' until the lack of approval of the County Society was called to its attention."

Elsewhere in this issue of the *Journal* a letter may be found from Dr. Paul R. Hawley, director of the American College of Surgeons, denying the allegation regarding oversight or falsification of the application to the College.

Another paragraph in the Columbia County Medical Society letter refers to a young physician in resident training at the Albany Hospital who was alleged to have been discouraged by the dean of the Albany Medical College "from locating in Germantown, presumably at the suggestion of Dr. Esselstyn, whose clinic plans to open a branch there."

Any attempt to influence this physician is specifically denied by Dr. Harold C. Wiggers, dean of the Albany Medical College, in a letter to the editor published in the *Journal* on September 10. A reply to Dr. Wiggers' letter by the physicians of Columbia County appears with Dr. Hawley's letter in the present issue, in company with a pertinent communication from an interested representative of the consumer group, Mr. C. G. Burke, of Ghent, New York.

Further information relating to the Rip Van Winkle Clinic has come to hand in the form of copies of letters approving the Clinic (which is licensed and approved as a dispensary by the Welfare Department of the State of New York) from the director of professional education of the American Cancer Society, Incorporated, the Health Information Foundation of New York, and the commissioner of health of the State of New York.

The *Journal*, having quoted in an editorial in the issue of July 30 the final phrase of the Columbia County physicians' letter of the same date "that *a group has the same responsibility and obligation to maintain medical ethics as does an individual practitioner*," finds that its employment of this axiomatic statement has been misinterpreted to the detriment of the Rip Van Winkle Clinic. The word *group* as used by the *Journal* was not intended to designate the Rip Van Winkle Clinic alone or any other specific organization for the practice of medicine. It may, indeed, be extended to include any aggregation of physicians, however organized, who might fall into the error of overlooking their moral obligations to the community and to their fellow practitioners.

Believing that both sides should be given an equal opportunity of expression where a difference exists, the *Journal* is now of the opinion that no further benefit can be derived from an extension in its columns of the discussion regarding medical practice in Columbia County, New York.

MEASLES ON VIRGIN SOIL

THE extreme contagiousness of measles can seldom be demonstrated these days, for in the ordinary course of events epidemics that make their rounds every other year or so permanently immunize most of the younger members of society.

The effect of measles on a population never previously exposed was demonstrated in the classic description of a pandemic outbreak in the Faroe Islands by Panum, an eyewitness of the great outbreak of 1846. More recently, Christensen and his colleagues reported an outbreak that swept through villages of Southern Greenland in the spring of 1951 after a young sailor, who imported the infection from Copenhagen, visited an infirmary in Julianehab on April 26 during the exanthematous stage of his infection.[1, 2]

The sailor, as sailors will, spent much of his time — and incidentally his most infectious period — roaming widely throughout the port and attended a "dancing-mik" on April 27 (a dancing-mik is presumably a strenuous affair, for within a week or two, 250 persons were down with the virus infection, a fact that gives some idea of potential infectivity in a virgin population). Altogether, 4221 of 4320 residents of Julianehab developed typical infection (giving an astounding attack rate of 97.6 per cent) and of the few who escaped, 31 persons had previously had measles during stays in Denmark.

Several unusual opportunities for the study of the natural history of measles were offered in the course of such a widespread outbreak. For example, all curves of incidence obtained from the larger villages of Greenland showed two large peaks after the source case or cases had been introduced, a fact that is readily understandable if each patient can potentially infect 100 or 200 other persons.

Eighty-three women suffered the disease in the course of pregnancy, mostly in the second half of gestation as far as could be determined (the native Greenland woman does not make special note of her first missed period). In 7 women the infections occurred during the puerperium; of the remaining 76, 26 promptly went into labor and produced 7 abortuses at three to five months, 6 prematurely born infants, of whom 3 died, and 13 infants born at term, of whom 2 died during the first twenty-four hours of life. A phenomenon similar to that which occurs after rubella during the first trimester of pregnancy was not observed: no congenital abnormalities occurred in the infants born of mothers who had contracted measles in early pregnancy. The number of cases is necessarily small, — only about 25, — but the implication is that measles either kills or spares the conceptus.

An interesting observation was made regarding tuberculosis morbidity. By sheer coincidence, a survey for tuberculosis had been completed in the village of Narssak in April just before the measles struck. Resurvey of 352 persons in September revealed 19 new patients with tuberculosis. Previously, 58 patients, 9 of whom had died after measles, had been detected. Thirteen of the 19 new patients showed positive sputums. The investigators had no hesitation in concluding that measles reduces resistance to tuberculosis.

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HANDS ACROSS THE ISTHMUS

THE Pan American Medical Association, no less than hemiglobal in its scope, was founded twenty-six years ago on the principle that "the practice of medicine has no national, racial or religious boundaries." Organized by a group of young physicians studying tropical medicine in New York in 1926, it has grown to an aggregation of 40,000 physicians representing 22 countries of the Americas. Nor is its influence confined to the terrestrial boundaries of these sovereign states; on water as well as on land it works unceasingly in the interests of medical culture.

Its avowed purposes are to promote closer relations among physicians in the countries represented, to develop postgraduate scholarships and to establish postgraduate teaching centers in the various countries of the Association. As a result of these developments three-year rotating scholarships will be awarded annually in such number that, at the end of the first three-year period, 198 physicians will be taking the courses of study, 66 returning each year to their own countries to practice and to teach.

In all, various years having been passed over and the war years having been perforce omitted, 8 Inter-American Medical congresses have been held. The ninth, another ship-to-shore convention, held largely under the aegis of Father Neptune, will convene on shipboard in New York on January 6, 1954, and will sail to conference meeting points in Caracas, San Juan, Ciudad Trujillo, St. Thomas and Havana. Holding brief authority even over Neptune, Dr. Pedro A. Gutiérrez Alfaro, Venezuelan Minister of Public Health and Welfare, the new president of the Association, will occupy the chair.

The newly-graduated Providence Thermometer is nearly ready for sale. Its main peculiarity is that zero represents blood heat.

Boston M. & S. J., *December 28, 1853*

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

PAYZANT—Claude L. Payzant, M.D., of Boston, died on December 5. He was in his sixty-seventh year.

Dr. Payzant received his degree from Boston University School of Medicine in 1910. He was on the staff of the Quincy City Hospital and was formerly president of the New England Physical Therapy Society.

He is survived by his widow and a son.

THORNE — Fred S. Thorne, M.D., of Boston, died on December 6. He was in his sixty-fourth year.

Dr. Thorne received his degree from Harvard Medical School in 1918. He was a member of the staffs of the Massachusetts Eye and Ear Infirmary, Symmes Arlington, Sancta Maria, Newton-Wellesley, Brooks and Carney hospitals, a fellow of the American Medical Association and the American Academy of Ophthalmology and Otolaryngology, and a former vice-president of the New England Ophthalmological Society.

He is survived by his widow and a sister.

MASSACHUSETTS DEPARTMENT OF MENTAL HEALTH

AGING POPULATION AND MENTAL HOSPITALS

Improved health of the population results in a larger number of aging persons and produces a new series of general, medical and sociologic problems. The mental health program to assure adequate coverage of this phase of the total problem must be re-examined.

The plan of management of mental hospitals has been changed by the increasing number of aged patients. These older patients are of two groups: those who grow old in the hospital, and those who are senile when admitted. Most large hospital systems were organized to meet the needs of young schizophrenic patients. The staffing patterns of the institutions were planned to use working squads to do much of the cleaning and maintenance work. The nursing service was set up to provide supervision for these occupational activities, only a few being needed to care for the bed patients. The food services were all set up around the cafeteria system. The bathing facilities were organized along the lines of those in the ordinary Y.M.C.A. or school shower room. The basic purpose of such organization was to provide the maximum amount of care at least possible cost, and with the fewest possible nursing and medical personnel. The need for constructive activity on the part of these patients was recognized and exploited to its fullest to afford the work opportunities mentioned above.

Improved treatment technics have upset the whole system. Almost all the manic-depressive patients who come to the hospital are treated and discharged within thirty to a hundred and twenty days. The variety of modern treatments for schizophrenia have by no means solved the problem, but they do succeed in turning out a large percentage of these patients, and the accumulation rate from schizophrenia is now small. Thus, improvements in treatment have resulted in a difficult economic situation. The older continued-care patients who at one time did a great deal of the simple work around the institution are now becoming too infirm, and former working colonies are gradually being converted into infirmaries to take care of the same patients. The difficulties are compounded. Patients who formerly required no bedside nursing now require such care, and in addition people must be employed to do the menial tasks formerly performed by the patients. This is not a sudden transition, but each year it is necessary to provide more infirmary beds, and supply larger proportions of bedside nursing care. Some hospitals are currently engaged in research projects directed toward chronic patients, principally those with schizophrenia. As these technics improve it is anticipated that still more of the so-called working group will become eligible for discharge to the community, still further compounding the nursing problem mentioned above.

Through the years there has been a gradual change in the types of patients. With improved mental health clinics and outpatient facilities, with a rise in the number of qualified psychiatrists practicing in the community and with an increasing awareness of the management of simple psychiatric problems on the part of the general medical practitioner, a good many of the severely neurotic, mildly depressed and early schizophrenic patients are cared for in the

community and are not referred to state mental hospitals. This is a tremendous step forward in the general health of the community, and one that should be exploited to its fullest. The number of severely disturbed schizophrenic patients seeking institutional care remains amazingly consistent through the years, irrespective of social and economic conditions. As mentioned above, a larger percentage of the newly admitted patients are dismissed. To offset these gains, rates of hospital admission continue to climb, consisting almost exclusively of older patients. In some large mental hospitals, as many as 35 and 40 per cent of the admissions are patients more than sixty years of age. In fact, with the improvement in discharge rates of the younger psychotic patients and in outpatient care both before and after hospitalization, the problem of overcrowding would have been solved medically, rather than structurally, if it had not been for the rise in the number of older patients. These elderly patients can be divided into the following three groups so far as their care is concerned, disregarding the detailed diagnostic criteria.

First, patients who are confused and also physically infirmed. Some have had strokes, and some show generalized weakness and debility. A few die shortly after admission; others may live for two or three years. The care of the physical infirmities of this group has greatly increased the use of consultations, in medicine, surgery and other specialties, and the Department is indeed grateful for the excellent co-operation of local medical groups in handling this phase of the problem.

Secondly, a large group of patients who come to the institution grossly psychotic because of organic disturbances in the brain; in spite of treatment they continue to be disturbed and psychotic. These patients are different from the first group, in that they are physically vigorous, and many of them live for years in the hospitals. Because they are physically vigorous, they adjust themselves reasonably well to general organization and nursing plans, but most of them are unable to work.

Thirdly, another large group of patients who come to the institution extremely confused or disturbed, but who show an improvement in mental symptoms with proper management of diet and correction of physical and dental infirmities. A good many can be returned to the community. The community will accept some of them back, but the families of others lack the resources or the desires to care for them. Some patients are placed in nursing homes and the family care program. A few prefer to stay in the mental hospitals because of the better medical care and the recreational facilities. This seems to be a matter of individual preference of the patient, some of them enjoying the security that they feel in the routine of institutional life. This group of patients is the one often described as "thousands of patients who do not need to be there." These statements are usually based on emotion rather than fact. With adequate supervision in the community many of these patients would get along; without it they would quickly become confused and irascible, and it would be necessary to go through the commitment process again. Improved resources in the community for nursing, recreational and family care, would increase the number of patients who could be dismissed. It should be pointed out, however, that the number of patients involved in this latter group is so small that their removal from the hospitals would not solve the nursing problem.

The majority of elderly patients come in the first two groups. It is obvious that any real solution of the problem will involve prevention, specialized facilities for care at the time of admission, improvement in the community resources and willingness of their families to accept them back after they have improved in the hospital.

These facts may be disconcerting unless viewed in proper historical perspective. An analogous situation that has been worked through involved patients with central-nervous-system syphilis. Forty years ago 10 to 15 per cent of the admissions to public mental hospitals were for some form of syphilis of the nervous system. Most of these patients died within two years of admission. The development of effective treatments for this form of syphilis compounded the difficulties temporarily, because all such patients were given these treatments. Patients with the early form were able to resume their places in the community. Large numbers, however, had the progress of their disease arrested, but did not show sufficient improvement to go back into the community, and stayed in the hospitals for many years. This resulted in an accumulation of chronic patients with syphilis of the brain and added to the nursing difficulties. With further education and emphasis on the early treatment of syphilis, and particularly with the development of the penicillin therapy of syphilis, this problem has been abolished. So few acute cases of syphilis of the nervous system are now encountered that it is difficult to find teaching material of this type. In the management of the problems of aging, medicine has advanced to the point where larger numbers of people are living to an old age, but no effective ways of keeping them in a vigorous productive state of health have been found.

The picture is not entirely negative, however. There are a number of hypotheses, some of which are workable. Some believe that the symptoms of senile dementia can be kept so mild that the person

can adjust himself in the community. All aging persons have periods of confusion, as well as periods when they become irritable and upset. These should be looked upon as normal symptoms of decreased adaptability, or decreased tolerance to frustration, closely akin to diminished cardiac reserve. It is also realized that these older persons cannot tolerate poor diet, toxic processes, loneliness, feelings of defeat and anxiety about their economic and social future. Clinics, such as those of Dr. Robert T. Monroe at the Peter Bent Brigham Hospital, demonstrate that patients who are properly supervised, with attention to these needs and protection from excessive or sudden demands on the part of the environment, can live out their life span without acute psychotic symptoms that make institutional care necessary. Although there is no specific proof, it is believed that persons who are kept constructively occupied show less tendency to deteriorate mentally. There is urgent need for carefully controlled epidemiologic studies in this area. It is hoped that such studies will be carried on here in the Commonwealth, and there is some indication that co-operative efforts will make them feasible. Since one is dealing with an aging organism, it would be fatuous to assume that any effort would totally resolve the problem. However, if 20 per cent of these cases could be prevented, it would be a tremendous boost to the general health and morale of the community, and incidentally would save the Commonwealth thousands of dollars a year in institutional care.

JACK R. EWALT, M.D.
Commissioner

CORRESPONDENCE

MORE ON RIP VAN WINKLE DISPUTE

To the Editor: The *Journal* has published two documents concerning the dispute between the Rip Van Winkle Clinic and certain physicians of Columbia County, New York. The first was a paper, "Group Practice with Branch Centers in a Rural Community," by Dr. Caldwell B. Esselstyn, in the issue of March 19, 1953. The second was a letter, in the issue of July 30, signed by twenty-five physicians of Columbia County. The first stated the purposes, aspirations, practices and history of the Rip Van Winkle Clinic, of which Dr. Esselstyn is medical director, in the city of Hudson in this county, and the second took issue with the first. Both documents are propaganda, as most of the Bible is, in that they try to convince readers of something. I have read both carefully, and several times, and if at the beginning I was certainly unbiased and entirely open to conviction by the more cogent presentment, whichever it might be, the conclusion of my study found me a partisan indeed.

Here are a few of the rhetorical and dialectical stratagems of the twenty-five ethicists in their attack on the Rip Van Winkle Clinic:

Paragraph 6. "Apparently as a subterfuge. . . ." Indictments are not based on "apparently." "Subterfuge" is in semantic distortion. The uncolored word "method" could have been used without affront to justice.

Paragraph 9. Contains a challenge to Dr. Esselstyn's veracity on the allocation of fees to doctors employed by the Clinic. His paper said that these men received a percentage; the letter says that he withheld a percentage from these men. This is remarkable as tautology in reverse, and reminiscent of the disputes of childhood. In view of its origin it is profoundly distressing. This paragraph also contains a boyish innuendo on the length and usefulness of luncheon conferences, and implies something invidious in the departure of doctors from the Clinic. But others not employed by the Clinic have departed this county and seventeen remain with the Clinic — by implication they must be knaves or dupes.

Paragraph 10. Exults that a publicity program sponsored by the American Cancer Society, to have featured the Rip Van Winkle Clinic, was suppressed by the Clinic's professional opponents. This seems hardly beneficial to the county as a whole, and the letter glides in this semantic perversion: "It has also been necessary to block other attempts at advertising." Advertising and publicity are not synonymous; publicity sponsored by an outside organization of austere credentials seems hardly heinous to those of us who fear cancer. The argument advanced by the twenty-five ethicists is censorious not only of the Rip Van Winkle Clinic and the American Cancer Society but also of the Mayo and Lahey clinics.

Paragraph 11. Utilizes "presumably" and "it appears" to establish a case injurious to Dr. Esselstyn. Bluntly, civilized society cannot accept such tactics from her responsible members.

Paragraph 12. "Dr. Esselstyn obviously aims to become the czar of medicine in Columbia County." No evidence is offered of what this means. "Czar" used like this plainly derives from the tabloid newspapers and is undefined and hence valueless. It implies something; what? And cannot twenty-five embattled ethicists prevent the usurpation?

Decidedly the dialectical method pursued by these doctors stifles their case in the fumes of ill feeling. If there is a valid objection to the procedures of the Rip Van Winkle Clinic, they have submerged it beneath a heap of trivia. Their letter has made of me, a neutral layman, a partisan in defense of an institution attacked not for what it is but for what it is insinuated to be.

For certainly this clinic has increased the medical resources of Columbia County. This, to a layman, is the important point. The twenty-five physicians, your correspondents, are pleased at having prevented the establishment of a cancer-detection center at the Clinic. We laymen, the potential beneficiaries, are less delighted at having such facilities halved. We should like to take comfort from a sense of medical adequacy.

Now a personal note to disarm innuendo perhaps to be directed at me. My household has received excellent and devoted medical care from the Clinic and from resident physicians hostile to the Clinic, including some who signed the lamentable letter. My personal physician, a signer, is still my personal physician although I utilize the Clinic for specialized services. This has not injured my health and I should think the interrelation not unhealthy for the profession of medicine in Columbia County. I write this letter voluntarily, without remuneration anywhere or instigation from the doctors in this dismal controversy. It is relevant perhaps to add that I may not be suspected of partiality for Dr. Esselstyn: we have enjoyed a reciprocally cool relation for some years. This cannot affect my wish to see justice done and fair play maintained and my neighbors' health protected.

C. G. BURKE

Ghent, New York

To the Editor: The doctors of Columbia County hesitate to prolong the controversy that appeared in recent issues of the *Journal*. Since Dr. Wiggers has used such terms as "loose and undocumented statement" and "irresponsible and unethical statement" in his letter appearing in the September 10, 1953, issue, a reply seems necessary.

First, we wish to make it clear that it was not our intention to jeopardize either the Albany Medical College or its administrative officer, but to show how one holding high office can be misled by Dr. Esselstyn into action helping his scheme.

The facts are as follows:

Dr. Esselstyn had a conversation with Dr. Wiggers concerning the young physician who planned to practice in Germantown, New York, well after the appearance of local newspaper accounts of Dr. Esselstyn's intentions to open a branch office in Germantown.

The young physician was called to Dr. Wiggers' office for an unsolicited interview.

In spite of the fact that Dr. Wiggers made no attempt to discourage or to encourage the young physician's decision to practice in Germantown, New York, the young physician was discouraged when he left Dr. Wiggers' office. In fact he was so much discouraged that he immediately sought the advice of a high-ranking member of the faculty.

I respectfully request that you publish this letter, which has been subscribed to by Drs. John L. Edwards, Carl G. Whitbeck, Ralph F. Spencer, Lawrence J. Early, Helen M. McEvoy, A. F. McEvoy, Leroy Holbert, Gene S. Rogati, Heinz Salm, Oscar Wilcox, Jr., H. J. Noerling, John Dardess, Leonard M. Niesen, Robert H. Little, Rosewell D. Shaw, Joseph P. Gold, Harold Levine, H. O. Little, A. F. White and R. L. Bowerhan.

HUGH G. HENRY, M.D.

Germantown, New York

To the Editor: In the July 30 issue of the Journal is printed a letter signed by a number of members of the Society of Medicine of Columbia County, New York.

In this letter the following statement is made: "Either through an oversight or through falsification of the application for approval, the American College of Surgeons carried this center (the Rip Van Winkle Clinic) on its 'Approval Lists' until the lack of approval of the County Society was called to its attention."

This statement is not correct. There was no falsification of the application for approval, nor was there any oversight on the part of the American College of Surgeons.

PAUL R. HAWLEY, M.D., *Director*
American College of Surgeons

Chicago, Illinois

PEDICULOSIS CILIORUM

To the Editor: In reference to the paper "Treatment of Pediculosis Ciliorum in an Infant," published in the *Journal* of November 26, may I say that, according to the United States of America Typhus Commission and in our own experience, cases of pediculosis ciliorum in infants are adequately and easily treated by lightly dusting a small amount of 10 per cent D.D.T. powder on the eyelashes of the child when he is asleep?

GEORGE H. FLESSAS, M.D.
Resident, Pediatric Service
Boston City Hospital

Boston

RESTORATION OF LICENSE

To the Editor: At a meeting of the Board of Registration held on October 22, 1953, it was voted that the registration of Dr. Z. Eileen Taylor, 15 Central Street, Winchester, be restored.

ROBERT C. COCHRANE, M.D.
Secretary

State House
Boston

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Man's Back. By Theodore A. Willis, M.D., consulting orthopedic surgeon, United States Public Health Service Hospital, Cleveland, Ohio. 4°, cloth, 161 pp., with 125 illustrations. Springfield, Illinois: Charles C Thomas, 1953. $9.50.

This monograph is devoted to a discussion of the normal and diseased back. The chapters present in order the embryology, anatomy, anomalies, mechanics, and examination, followed by injuries, diseases, tumors, scoliosis, psychoneuroses and malingering, physical therapy and operations. The text is well illustrated; there is a good index, and the publishing is excellent. The book should be in all collections on orthopedics and surgery.

Die neuzeitlichen Brustwand- und Extremitäten-Ableitungen in der Praxis. By Prof. Dr. Herbert Reindell, chief physician, Medizinischen Universitätsklinik Freiburg i. Br.; and Dr. Helmuth Klepzig, assistant, Medizinischen Universitätsklinik Freiburg i. Br. With a foreword by Prof. Dr. Ludwig Heilmeyer, director, Medizinischen Universitätsklinik Freiburg i. Br. Second edition. 8°, cloth, 188 pp., with 70 illustrations. Stuttgart: Georg Thieme, 1953. DM 24.60. (Distributed by Grune and Stratton, New York).

The first edition of this monograph was published in 1951. The author has revised and brought his text up to date. The literature is surveyed and a bibliography of 13 pages is appended to the text. The book should be in collections on electrocardiography.

Emotional Factors in Skin Disease. By Eric Wittkower, M.D., and Brian Russell, M.D. With contributions from Peter Edgell, Desmond Irwin and John Slorach, and with forewords by Dr. R. M. B. Mackenna and Professor D. E. Cameron. 8°, cloth, 214 pp., with 17 tables. New York: Paul B. Hoeber Incorporated, 1953. $4.00. (*A Psychosomatic Medicine Monograph.*)

This composite monograph is the joint work of 5 physicians, who discuss the psychosomatic aspects of diseases of the skin. The text is divided into two parts, general and specific. The general part deals with the psychosomatic approach, development, neuroanatomy and physiology of the skin, and investigation and management of patients. The special part is devoted to abnormal skin sensation and manifestations and psychoses. Lists of references are appended to the chapters and to special diseases, and there is a survey of pertinent literature. There are indexes of authors and subjects, and the publishing is good. The monograph should be in collections on dermatology and nervous and mental diseases.

Essential Urology. By Fletcher H. Colby, M.D., chief, Urological Service, Massachusetts General Hospital, associate clinical professor of genitourinary surgery, Harvard Medical School, and urological consultant, Lakeville Sanatorium, Middleboro, Massachusetts. Second edition. 8°, cloth, 650 pp., with 352 illustrations. Baltimore: Williams and Wilkins, 1953. $8.00.

The first edition of this book was published in 1950 and reprinted twice. The text has been revised and brought up to date. The chapters on diseases of the prostate and testis and on tuberculosis have been thoroughly revised. Lists of references are appended to the chapters, and many new references have been included in this new edition. The book reflects the practice of urology as carried out at the Massachusetts General Hospital. There is a good index, and the publishing is excellent. The book should be in all medical libraries and in the libraries of urologists.

The Use of Drugs: A textbook of pharmacology and therapeutics for nurses. By Walter Modell, M.D., assistant professor, Cornell University Medical College; and Doris J. Place, R.N., instructor in medical nursing, Cornell University New York Hospital School of Nursing. 8°, cloth, 468 pp. New York: Springer Publishing Company, Incorporated, 1953. $4.50.

This new book on drugs, which is intended for nurses, should also be of interest to physicians. The text is divided into 4 parts: the principles of pharmacology; principles of therapeutics; medicine; and materia medica. The third part contains valuable information on medical English and Latin, weights and measures, medical arithmetic and procedures in dosage calculation and the preparation of solutions. The last part, comprising 129 pages, consists of an alphabetical list of drugs of all types, with their descriptions, action and uses, and administration and other information. This is a valuable list that could be used to advantage by the medical librarian as a quick reference source. There is a good index, and the publishing is excellent.

NOTICES

HARVARD MEDICAL SOCIETY

A meeting of the Harvard Medical Society will be held in the main amphitheater of the Peter Bent Brigham Hospital on Tuesday, January 12, at 8 p.m. George W. Thorn will preside. The program will be as follows:

Hydraulic Principles Governing the Circulation in Aortic Valvular Diseases. Richard Gorlin.

Body Composition as Revealed by Isotope Dilution: A status report and a description of the "syndrome of depletion." Francis D. Moore, Isidore S. Edelman, Graham M. Wilson, Caryl Magnus and Margaret R. Ball.

The Effect of Small Hypothalamic Lesions on Compensatory Adrenal Hypertrophy. William F. Ganong and David M. Hume.

Recent Studies of Hyperadrenocorticism: Its pathologic physiology and management. John C. Laidlaw, Hartwell Harrison and George W. Thorn.

Psychiatry in Surgery: A beginning approach in the field of gynecology. Somers H. Sturgis and Doris Menzer.

Cerebral Circulation in Pernicious Anemia. Eugene Robin, Frank H. Gardner, John R. Tyler, C. Sidney Burwell and James Metcalfe.

SOUTH END MEDICAL CLUB

A meeting of the South End Medical Club will be held at the headquarters of the Boston Tuberculosis Association, 554 Columbus Avenue, on Tuesday, January 19, at 12 noon. Dr. R. Adelaide Draper will speak on the subject "Orientation in Postgraduate Medical Education." All physicians are cordially invited.

ROTATING INTERNSHIP, SAINT ELIZABETHS HOSPITAL

The United States Civil Service Commission has announced a new examination for medical officer, to fill the position of rotating intern, at $2800 a year, in Saint Elizabeths Hospital, Washington, D. C. Applications will be accepted by the Executive Secretary, Board of U. S. Civil Service Examiners, Saint Elizabeths Hospital, Washington 20, D. C.

SOCIETY MEETINGS AND CONFERENCES

JANUARY 4. New England Cardiovascular Society. Page 1004, issue of December 10.

JANUARY 4. American Federation for Clinical Research, Eastern Sectional Meeting. Page 1044, issue of December 17.

JANUARY 6, MARCH 3 and APRIL 21. Massachusetts Society for Research in Psychiatry. Page 750, issue of October 29.

JANUARY 12. Harvard Medical Society. Page 1087.

JANUARY 13. Boston Gastroenterological Society. Page 1044, issue of December 17.

JANUARY 19. South End Medical Club. Notice above.

JANUARY 22, 23, 29 and 30. International College of Surgeons Regional Meeting. Page 828, issue of November 12.

JANUARY 26. Massachusetts Hospital Association. Hotel Statler, Boston.

FEBRUARY 2–4. Examination for Public Health Service Medical Officers. Page 750, issue of October 29.

FEBRUARY 5 and APRIL 9. New England Society of Anesthesiologists. Page 914, issue of November 26.

FEBRUARY 15–20. Pan-American Academy of General Practice. Page 790, issue of November 5.

FEBRUARY 23–25. College of Medical Evangelists Alumni Postgraduate Convention. Page 1044, issue of December 17.

MARCH 15–26. Course in Laboratory Diagnosis of Virus Diseases. Page 1044, issue of December 17.

MARCH 27 and 28. American Psychosomatic Society. Page 1044, issue of December 17.

MAY 14–16. Fifth Annual International Group of Doctors in Alcoholics Anonymous. Page 1004, issue of December 10.

MAY 31–JUNE 3. American Urological Association. Page xvii, issue of July 23.

JULY 22 and 23. International College of Surgeons Regional Meeting. Page 828, issue of November 12.

JULY 23–29. International Cancer Congress. Page 914, issue of November 26.

SEPTEMBER 7–10. Nineteenth Annual Congress of the United States and Canadian Sections of the International College of Surgeons. Page 828, issue of November 12.

SEPTEMBER 12–15. Second International Congress of Cardiology. Page 44, issue of July 2.

SEPTEMBER 16–18. American Heart Association Annual Scientific Sessions. Page 44, issue of July 2.

DISTRICT MEDICAL SOCIETIES

ESSEX NORTH

JANUARY 13. Pentucket Club, 111 Main Street, Haverhill.

MAY 12. 113th Annual Meeting. Andover Country Club, Andover.

MIDDLESEX EAST

JANUARY 20. (Combined with the Auxiliary.)

MARCH 24.

MAY 11. Annual Meeting. (Harlow Dinner.)

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, DECEMBER 31

THURSDAY, DECEMBER 31

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.

10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.

*5:00–6:00 p.m. Surgical Division Meeting. Mount Auburn Hospital, Cambridge.

FRIDAY, JANUARY 1

Holiday.

SATURDAY, JANUARY 2

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.

*9:00 a.m. Proctology Clinic. Peter Bent Brigham Hospital.

*9:00 a.m. Alcoholism Clinic. Peter Bent Brigham Hospital.

10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

11:00 a.m.–12:00 m. Blood Clinic. Dr. William Dameshek. Stearns Auditorium, New England Center Hospital.

MONDAY, JANUARY 4

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*8:00–9:00 a.m. Medical and Surgical Clinic on Diabetic Foot Problems. New England Deaconess Hospital.

8:30–9:30 a.m. Clinic by entire Surgical Staff and Anesthesia Staff. Cheever Amphitheater, Dowling Building, Boston City Hospital.

9:00 a.m. American Federation for Clinical Research. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.

10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

12:00 m. Clinicopathological Conference (Boston Floating Hospital). Pratt Lecture Hall. Joseph H. Pratt Diagnostic Hospital.

*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.

7:00–9:00 p.m. Combined Anesthesia Resident Training Program. Jimmy Fund Auditorium, Children's Medical Center, 35 Binney Street.

*8:00 p.m. New England Cardiovascular Society. Morse Auditorium, Museum of Science.

TUESDAY, JANUARY 5

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*9:00 a.m. Geriatrics Clinic. Peter Bent Brigham Hospital.

10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*12:00 m. Pediatric Grand Rounds. Cheever Amphitheater, Dowling Building, Boston City Hospital.

*12:00 m.–1:00 p.m. Pediatric Rounds. Burnham Memorial Hospital for Children, Massachusetts General Hospital.

*12:15–1:15 p.m. X-ray Conference. Dr. Merrill Sosman. Main Amphitheater, Peter Bent Brigham Hospital.

*12:30–1:30 p.m. Medical Journal Club. Cafeteria, New England Deaconess Hospital.

*4:30–5:30 p.m. Anesthesia Teaching Conference. Stearns Auditorium, New England Center Hospital.

*5:00 p.m. Surgical Journal Review. Mount Auburn Hospital, Cambridge.

*5:00–6:00 p.m. Service Meeting followed by Clinical Conference (Medical, Surgical, Obstetrical), Faulkner Hospital.

WEDNESDAY, JANUARY 6

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*12:00 m. Boston State Hospital Psychiatric Seminar. Reception Building Auditorium, 591 Morton Street, Dorchester.

*12:00 m.–1:00 p.m. Clinicopathological Conference. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.

*12:30 p.m. Weekly Pathological Meeting. Joslin Auditorium, New England Deaconess Hospital.

12:30–1:30 p.m. Weekly Staff Review of Autopsies. Dr. William A. Meissner. Joslin Auditorium, New England Deaconess Hospital.

*1:30–2:30 p.m. Pathological Conference. Dr. C. Jones. Nurses' Home, Cambridge City Hospital.

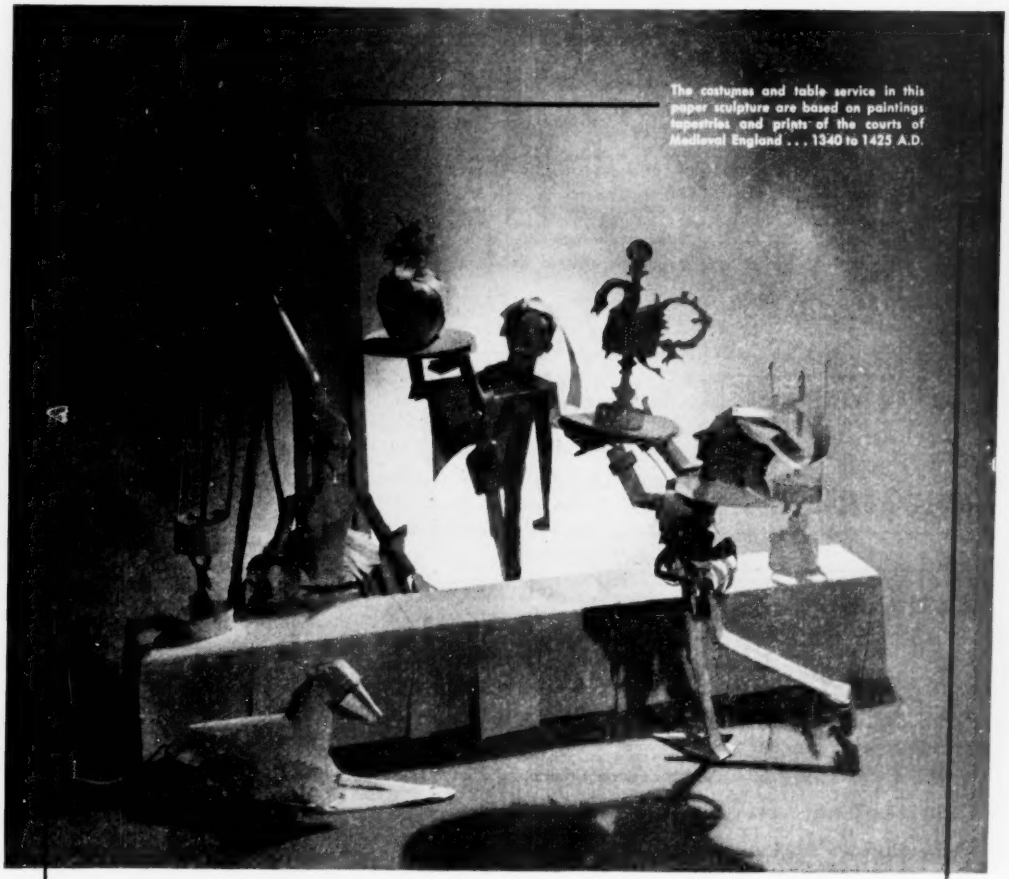
2:00–3:00 p.m. Pediatric Conference for Practitioners. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.

*4:00–5:30 p.m. Fracture Lecture. Boston City Hospital.

*4:00–6:00 p.m. Overholt Thoracic Conference. Joslin Auditorium, New England Deaconess Hospital.

*5:00–6:00 p.m. American Cancer Society Telecast. Diagnosis and Treatment of Uterine Cancer. Dr. Howard C. Taylor, Jr. Children's Cancer Research Center, 35 Binney Street.

*Open to the medical profession.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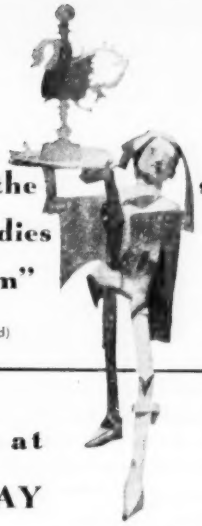

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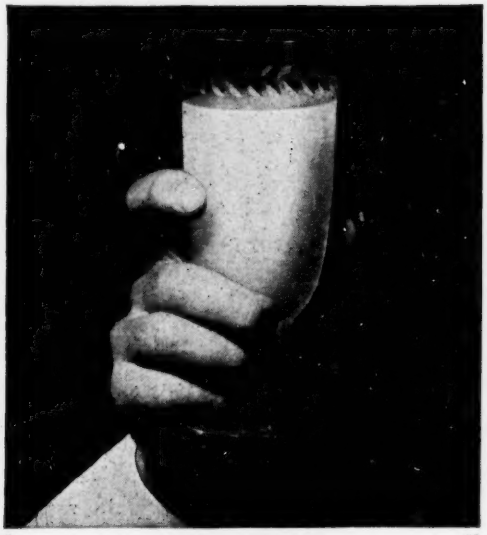

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1. Reich, C., and Mullnos, M. G., Treatment of Refractory Nutritional Anemia with Gelatine. Bull. N.Y. Med. Coll. March 1953.

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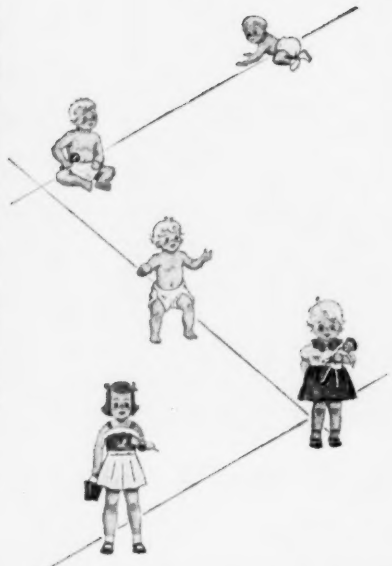

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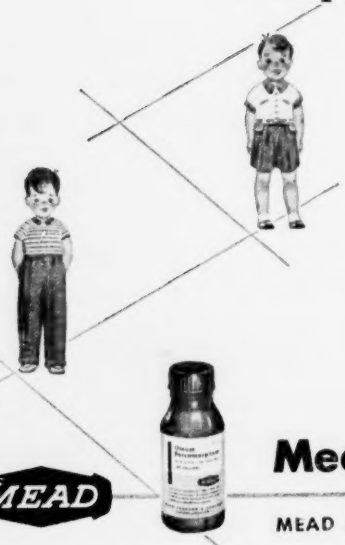

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